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GASTRIC HAEMORRHAGE IN ACUTE INTRACRANIAL VASCULAR ACCIDENTS[1]

By A. DOIG and J. SHAFAR

(From the Burnley Group of Hospitals, Lancs.)

With Plates 1 to 3

The occurrence of acute lesions of the gastrointestinal tract in association with intracranial disease has been recognized since the first half of the nineteenth century (Camerer, 1828; Andral, 1831, 1840; Rokitansky, 1842; Siebert, 1842). Although this subject has received much attention in the more recent Continental and American literature, it is one which has been strangely neglected by British clinicians and pathologists. The lesions of the digestive tract may take the form of mucosal haemorrhages, erosions, or acute ulcers. They are found most commonly in the stomach, and especially in the fundal region; the duodenum and lower oesophagus are not infrequent sites of occurrence, while involvement of the remainder of the small intestine or the large intestine has rarely been reported. A further type of lesion described is that of gastromalacia; applied to gross morbid appearances, this term serves to differentiate a large and often poorly demarcated area of dissolution from the small, sharply circumscribed, punched-out ulcer (Schlumberger, 1951). As regards the associated lesions of the central nervous system, examples of nearly all types of intracranial disease have been reported; they have been more frequently acute than chronic, and in the case of new growths the majority of reports give a history of a recent acute episode, either operative interference or spontaneous haemorrhage into the growth.

The acute lesions of the digestive tract may be complicated by haemorrhage or perforation, thus allowing clinical recognition. Thus haematemesis and melaena have been reported in the following conditions:

Intracranial neoplasm (von Winiwarter, 1911; Hallé and Lereboullet, 1931; Cushing, 1932; Masten and Bunts, 1934; Bodechtel, 1935; Grant, 1935; Swan and Stephenson, 1935; Davies, 1936; Dott, 1938; Ask-Upmark, 1939; Davidoff, 1944; Fugazzola, 1947; Mossberger, 1947; Nitshe and Suckle, 1947; Bastenie, Desneux, and Kowalewski, 1949; Laruelle and Reumont, 1949; Fisher, Watkins, Gardner, and Klotz, 1951; Globus and Ralston, 1951; Gray, Benson, Reifenstein, and Spiro, 1951; French, Porter, von Amerongen, and Raney, 1952; King and Reganis, 1953; Davis, Wetzel, and Davis, 1955).

Meningitis (Gerdine and Helmholz, 1915; Hart, 1919; Bodechtel, 1935; Opper and Zimmerman, 1938; Letondal, 1940; Benner, 1943; Fuertes, 1943; Picard, Charbonnel, and Giraudet, 1948).

[1] Received June 22, 1955.

Head injury (Opper and Zimmerman, 1938; Vanzant and Brown, 1938; Ask-Upmark, 1939; Wyatt and Khoo, 1949; French, Porter, von Amerongen, and Raney, 1952).

Bulbar poliomyelitis (Erskine, Mason, and McDade, 1950; Cook, Hartmann, Sarnoff, and Berenberg, 1951; Lenarsky, Parr, and Seanor, 1951; Schlumberger, 1951; Baker, Cornwell, and Brown, 1952; Baker, Brown, and Cornwell, 1952; Hoxsey, 1953; Schaberg, Hildes, and Alcock, 1954).

Intracranial haemorrhage of the newborn (Spiegelberg, 1869; Genrich, 1877; Pomorski, 1891–2; von Preuschen, 1894; Schweizer, 1896; Gottlieb, Chu, and Sharlin, 1950).

Cerebral infarction (Bodechtel, 1935; Reese and Masten, 1948; French, Porter, von Amerongen, and Raney, 1952; Sarason and Levy, 1954).

Intracranial aneurysm (Cachera, Duval, and Scherrer, 1944).

Encephalitis (Picard, Charbonnel, and Giraudet, 1948).

Choreo-athetosis (Babonneix and Lévy, 1931).

Cerebellar cyst (French, Porter, von Amerongen, and Raney, 1952).

After frontal lobotomy (Sweet, Cotzias, Seed, and Yakovlev, 1948; French, Porter, von Amerongen, and Raney, 1952).

After pneumoencephalography (Masten and Bunts, 1934; Bodechtel, 1935).

We describe seven cases of gastric haemorrhage, each of which occurred in association with a spontaneous intracranial haemorrhage. There was clinical evidence of bleeding in the alimentary tract in six instances, and in the seventh case blood was found in the stomach at autopsy. Previous reports of acute gastroduodenal lesions associated with spontaneous intracranial haemorrhage have been published by Andral (1840), Charcot (1886), Lépine (1895), von Czyhlarz (1912), Hart (1913, 1914, 1919), Masten and Bunts (1934), Daniels (1934), Bodechtel (1935), Opper and Zimmerman (1938), Vonderahe (1939), Baló (1941), Davidoff (1944), Strassmann (1947), Betz (1949), Staemmler (1949), Wyatt and Khoo (1949), Freisinger, Lapis, and Baló (1950), Globus and Ralston (1951), French, Porter, von Amerongen, and Raney (1952), and Fletcher and Harkins (1954). Haematemesis was noted in only eight of these cases, the total of which exceeds 60 (von Czyhlarz, 1912; Hart, 1913; Daniels, 1934; Bodechtel, 1935; Freisinger, Lapis, and Baló, 1950; Globus and Ralston, 1951; French, Porter, von Amerongen, and Raney, 1952). We also report the results of a special histological study of the stomach, undertaken to elucidate some of the local factors which are involved in the production of erosions and acute ulcers.

Case 1. Subarachnoid haemorrhage with haematemesis as the presenting feature

A woman aged 76 years suddenly developed severe frontal headache and nausea on April 3, 1954. Half an hour later she vomited 'brown fluid' and felt faint; she was forthwith removed to hospital. After vomiting 'coffee-ground' material in the casualty department, she was referred for admission as a case of haematemesis. There was no previous history of dyspepsia. On examination she was pale, with a clammy skin, and fully conscious. The pulse and respiration rates were 124 and 24 per minute respectively; the temperature was 97·5° F., and the blood-pressure 160/100. There was epigastric tenderness, but no other abnormal findings on abdominal examination. Examination of the central nervous system was negative, and apart from numerous extrasystoles there were no other abnormal findings on physical examination. The following

day the patient became drowsy, and while asleep exhibited Cheyne-Stokes respiration. There was further vomiting, and on this day some unaltered blood was seen among the 'coffee-grounds'. The haemoglobin was 11·7 gm. per 100 ml., white-cell count 13,000 per c.mm., and blood-urea 84 mg. per 100 ml. On the third day the temperature began to rise, and there was an increase in the pulse and respiration rates; crepitations appeared in the lung bases. Systemic penicillin was given. In the course of the next few days the patient slowly lost consciousness, her tendon-reflexes disappeared, and the plantar responses became extensor. There was no evidence of further bleeding from the gastro-intestinal tract. She died in coma on the sixth day after admission.

Autopsy was performed eight hours after death. The subarachnoid space contained a large amount of blood-clot, most of which was situated at the base of the brain. The brain on section presented no abnormalities. Examination of the alimentary tract failed to reveal any macroscopic lesion. Both lungs were congested, and the right lower lobe was consolidated. The heart showed slight left ventricular hypertrophy. Microscopically the stomach showed numerous small areas of mucosal damage, in which there was evidence of commencing repair (Plate 2, Fig. 5). The alveoli in the consolidated lobe of the lung were filled with an exudate of polymorph leucocytes. The pituitary and adrenal glands appeared normal.

Case 2. Cerebral haemorrhage. Haematemesis one and a half hours after the onset

A woman aged 41 years was admitted to hospital in coma on November 25, 1953. While at work as a weaver in a cotton mill, approximately one and a half hours prior to admission, the patient complained of the sudden onset of weakness in the right arm, and shortly afterwards lost consciousness. Within an hour of the loss of consciousness she began to vomit bright red blood. A history was obtained of left hemiparesis of rapid onset four months previously; the hemiparesis had cleared spontaneously, and she had been able to resume work three weeks after the onset. On examination she was restless, and breathing stertorously; the face was flushed, and the pulse and respiration rates were 110 and 30 per minute respectively. The temperature was 98·0° F., and the blood-pressure 190/160. She vomited again immediately after admission. On this occasion the vomitus consisted of 'coffee-grounds' streaked with unaltered blood. Neck rigidity and Kernig's sign were both present, and the patient exhibited the features of decerebrate rigidity. The tendon-reflexes were brisk and bilaterally equal, and both plantar responses were extensor. There were no abnormal findings in the other systems. Lumbar puncture yielded blood-stained fluid under a pressure of 210 mm. The patient's condition deteriorated, and Cheyne-Stokes respiration developed; death occurred eight and a half hours after admission.

Autopsy was performed six hours after death. There was a small amount of blood-stained fluid in the stomach. The gastric mucosa showed numerous petechial haemorrhages and ecchymoses; these were mainly confined to the proximal half of the organ, and along the lesser curvature they occupied the crests of the mucosal folds (Plate 1, Fig. 4). The pyloric canal was notably free from haemorrhage. Aggregations of petechiae were present in the mucosa of the first part of the duodenum. The subarachnoid space contained a small amount of semi-fluid blood-clot. Section of the brain revealed a large haemorrhage in the left cerebral hemisphere; this involved the corpus striatum, thalamus and hypothalamus, the lateral and third ventricles, and the cerebral white matter. In the right internal capsule there was a small area of softening. The heart showed a moderate degree of left ventricular hypertrophy. Microscopically

the pituitary showed congestion of the sinusoids; the adrenal glands were normal. The arterioles of the kidneys showed the features of early diffuse hyperplastic sclerosis.

Case 3. Subarachnoid haemorrhage and transient hyperglycaemia. Haematemesis eight hours after the onset of coma. Recovery

A housewife aged 57 years was found unconscious at her home on December 21, 1954, and was shortly afterwards admitted to hospital. At the time of admission the duration of coma was estimated to be one hour. The patient had previously been in good health. The pulse-rate was 110 per minute, and there were frequent extrasystoles; the temperature was 96·0° F., and blood-pressure 220/120. There was marked nuchal rigidity, and Kernig's sign was positive. The limbs were flaccid, and all the deep reflexes were absent; both plantar responses were extensor. There were no abnormal signs referable to the cranial nerves. Apart from osteoarthritis of both knees, the remainder of the physical examination was negative. The urine was found to contain both sugar and acetone; there was no albuminuria. The blood-sugar level was 277 mg. per 100 ml., and blood-urea 44 mg. per 100 ml. On lumbar puncture the cerebrospinal fluid was heavily blood-stained, and the pressure was 125 mm. Seven hours after admission the patient began to vomit 'coffee-ground' material; this gave a strongly positive benzidine reaction. During the next 36 hours she continued to vomit altered blood at frequent intervals, and slowly regained consciousness. The faeces gave a positive reaction for occult blood on 23.12.54 and 28.12.54, and negative reactions were obtained on 30.12.54 and on four subsequent occasions. The glycosuria, which was initially estimated at 1 to 2 gm. per 100 ml., rapidly decreased in amount after 48 hours, and disappeared in the course of the next fortnight. At the time of her discharge from hospital on 29.1.55 no abnormal physical findings were evident beyond that of hypertension. Radiological examination of the oesophagus, stomach, and duodenum on 24.1.55 failed to reveal any evidence of ulceration. An X-ray of the chest showed a moderate degree of left ventricular enlargement. A glucose-tolerance test on 28.1.55 produced a normal curve. A fractional test meal showed free hydrochloric acid rising to a maximum of 65 mEq. per litre at two hours.

Case 4. Cerebral haemorrhage. Haematemesis shortly after the onset

A woman aged 44 years, known to be hypertensive, was admitted to hospital in coma on November 1, 1954. She had been found one hour previously lying on a couch in a semi-comatose state, vomiting bright red blood. Fifteen minutes before she was discovered in this condition the patient had been seen by her son, who had observed nothing untoward. During transit to hospital the patient continued to vomit, and saturated a towel with blood. There was a history of a right hemiparesis 15 months previously, followed by a recurrence two months later. After the latter incident the patient had been admitted to hospital for treatment of her hypertension; hypotensive drugs were administered, but were discontinued several months later because of poor response. On examination blood was trickling from the mouth; the patient was restless, and breathing was stertorous. The pulse and respiration rates were 102 and 24 per minute respectively; the temperature was 96·0° F., and blood-pressure 260/150. There was a left facial paralysis, and marked rigidity of the left upper and lower limbs. All the deep reflexes were absent, and the plantar reflexes were both extensor. Both pupils were dilated and did not react. The fundi showed a grade II hypertensive retinopathy. Apart from lateral displacement of the cardiac apex beat, there were no abnormal findings in the other systems. After a period of extreme

restlessness the patient died, four hours after admission, without regaining consciousness.

Autopsy was performed 12 hours after death. The stomach contained a small quantity of dark red blood. The entire gastric mucosa was congested, and there were numerous punctate haemorrhages and small haemorrhagic erosions in the mucosa of the fundus and cardia. Section of the brain revealed a large haemorrhage involving the right corpus striatum and both lateral ventricles (Plate 1, Fig. 2). Blood was present in the third and fourth ventricles and in the aqueduct. Small cystic areas were found in the left internal capsule and putamen, and in the right putamen. The lungs were congested, and the heart showed a considerable degree of left ventricular hypertrophy. The kidneys were of normal size, and presented a finely granular surface; microscopically they showed the features associated with essential hypertension. There was no histological abnormality of the hypothalamus, pituitary, or adrenals.

Case 5. Pontine haemorrhage. Haematemesis one hour after the onset

A retired labourer aged 68 years was admitted to hospital on November 27, 1954 in coma. Approximately one hour prior to admission he had experienced difficulty with speech, and shortly afterwards had lost consciousness. Five years previously he had had a brief loss of consciousness, which was followed by a period of mental confusion lasting several weeks. Since this episode he had suffered from several transient attacks of loss of consciousness which were succeeded by facial asymmetry and slurring of speech. On examination he was vomiting 'coffee-ground' material, which gave a positive reaction on being tested for blood. Breathing was stertorous, and the pulse and respiration rates were 84 and 26 per minute respectively; the temperature was 97·4° F., and blood-pressure 215/140. There was a left internal strabismus, and both pupils were minutely contracted. There was slight spasticity, and an increase in the deep reflexes, in the right upper and lower limbs; an extensor plantar response and ankle clonus were also elicited on the right side. The patient was incontinent of urine. There were no abnormal findings on examination of the other systems. Lumbar puncture yielded slightly blood-stained cerebrospinal fluid with a pressure of 130 mm. During the next few hours the patient vomited 350 ml. of altered blood. Death occured 19 hours after admission.

Autopsy was performed two and a half hours after death. The internal surface of the stomach was covered with mucus, which contained a mixture of fresh and altered blood; the gastric mucosa was congested and, in the proximal two-thirds of the organ, presented a large number of punctate haemorrhages, which were especially prominent along the ridges of the mucosal folds. Section of the brain revealed a haemorrhage occupying the greater part of the pons (Plate 1, Fig. 3), which had ruptured into the fourth ventricle. This haemorrhage extended into the left basis pedunculi and the left middle cerebellar peduncle. The fourth ventricle was distended with blood-clot; in the right thalamus there was a small area of softening. The heart showed a moderate degree of left ventricular hypertrophy. Microscopic examination of the hypothalamus showed congestion of the capillaries and small veins. The small vessels of the kidneys showed hyaline degeneration, and there was occasional glomerular fibrosis. The pituitary and adrenal glands showed no significant abnormality.

Case 6. Cerebral haemorrhage. Occult blood in faeces 20 hours after the onset

A labourer aged 49 years was admitted to hospital on October 21, 1954, one hour after the sudden onset of loss of consciousness. Eighteen hours previously he had 'collapsed' in the street and had to be escorted home. At that time he

complained of right-sided headache and nausea. The patient had been mentally dull since childhood, and the right eye was congenitally absent. His physical health had always been good. On examination he was deeply unconscious, the skin was pale and clammy, and there was Cheyne-Stokes respiration. The pulse rate was 110 per minute, blood-pressure 170/80, and temperature 100·0° F. There were the features of decerebrate rigidity. The left pupil was contracted, and did not react to light. Examination of the faeces for occult blood gave a strongly positive result. The patient died four and a half hours after admission.

Autopsy was performed three hours after death. The stomach contained a small quantity of altered blood; in the mucosa of the cardia, fundus, and proximal part of the body there were numerous superficial erosions 2 to 5 mm. in diameter, punctate haemorrhages, and ecchymoses. The remainder of the alimentary tract presented no abnormality. Examination of the brain revealed a bulky right cerebral hemisphere; on section it was found to contain a massive haemorrhage, which occupied its greater part. There was considerable haemorrhagic destruction of the basal ganglia, thalamus, and hypothalamus. There was right anophthalmos, with fusion of the eyelids; the right optic nerve was represented by a thin fibrous cord. Both lung bases were congested. The heart and kidneys were normal. Microscopic examination of the pituitary and adrenal glands revealed no abnormality.

Case 7. Cerebral haemorrhage. Post-mortem finding of gastric haemorrhage

A woman aged 65 years, known for 13 years to be diabetic, was admitted to hospital on November 11, 1954 in an unconscious state. She had appeared in good health until three hours prior to admission, when she complained of nausea and vomited a few ounces of bile-stained fluid. The diabetes had always been mild, and she had never required insulin. The patient had recently suffered from a right herpes ophthalmicus. On examination she was breathing stertorously. The pulse and respiration rates were 60 and 30 per minute respectively, temperature 99·0° F., and blood-pressure 180/80. The pupils did not react to light. There was generalized muscular flaccidity, and the deep reflexes were sluggish. Both plantar responses were flexor. The urine contained a trace of sugar, and no acetone. The blood-sugar was 40 mg. per 100 ml., and blood-urea 16 mg. per 100 ml. Lumbar puncture yielded blood-stained cerebrospinal fluid under a pressure of 165 mm. Death occurred 12 hours after admission.

Autopsy was performed six hours after death. The stomach contained 20 ml. of dark red blood; there was extensive involvement of the mucosa with petechial haemorrhages and ecchymoses, the principal distribution of the lesions being in the fundus and lesser curvature. In the left cerebral hemisphere there was a massive haemorrhage involving the temporal lobe, corpus striatum, thalamus, and hypothalamus. The third and fourth ventricles were distended with blood-clot. The heart showed a moderate degree of left ventricular hypertrophy. The other organs appeared healthy.

Pathology of the Stomach Lesions

The mucosal haemorrhages, erosions, and acute ulcers of the stomach found in association with intracranial disease do not differ in their gross or microscopic appearances from those found in patients without disease of the central nervous system, or from those produced in animals by various experimental means. The initial lesion observed in the mucosa is either a small area of haemorrhage or an area of ischaemic necrosis, the former being the more common type of lesion.

The haemorrhages are usually situated superficially in the mucosa, and when well formed are wedge- or cone-shaped, the base being on the free surface of the mucosa; less commonly the areas of haemorrhage occur in the deeper aspects of the mucosa, and in this situation they are usually irregular in shape. Not infrequently both superficial and deep mucosal haemorrhages are found in the same specimen. Ivy, Grossman, and Bachrach (1950) have called these two types of haemorrhage 'primary interstitial haemorrhage followed by necrosis', and they are distinguished from a third type of mucosal haemorrhage, occurring as a secondary feature in an area of anaemic necrosis—'primary necrosis followed by interstitial haemorrhage'. Sloughing or digestion of the necrotic or damaged mucosa produced by the early lesions results in the formation of an erosion or, if the muscularis mucosae is penetrated, an acute ulcer. The formation of an erosion or an acute ulcer from a mucosal haemorrhage has been observed under direct vision in experimental animals (Roth and Ivy, 1945) and gastroscopically in the human subject (Jones, 1947). Early histological studies, with detailed descriptions of the process in dogs and rabbits, were made by Schiff (1867). Histological observations in human material have been recorded by Hagemann (1909), Nicolaysen (1920), Robertson (1939), Merkel (1944), Staemmler (1949), and others. It will be appreciated from the foregoing observations that a study of the formation of a mucosal haemorrhage is of fundamental importance in the pathogenesis of erosions and acute ulcers. Since a knowledge of the vascular anatomy of the gastric mucosa is necessary for the further consideration of this subject, we offer a brief description of the mucosal blood-supply. We have summarized the arrangement of the arteries and capillaries from the results of the studies with injection and microradiography made by Barlow, Bentley, and Walder (1951), while the micro-anatomy of the veins is based on the descriptions of Hagemann (1909) and supplemented by our own observations.

The mucosal arteries in the anterior and posterior walls of the stomach arise from an arterial plexus situated in the submucosa; in the region of the lesser curve, however, the mucosal arteries do not arise from such a plexus, but have their origin outside the stomach directly from the right and left gastric arterial chain. As each mucosal artery approaches the muscularis mucosae it divides into two to three smaller branches, which pierce the muscular layer (Fig. 1). In the region immediately below the muscularis mucosae there is a free anastomosis between adjacent mucosal arteries and their branches. Having pierced the muscularis mucosae, the mucosal branches form an anastomotic channel on its mucosal aspect, and then split up into leashes of capillaries which run vertically towards the surface. From the vertical vessels smaller capillaries arise, which ramify among the glands and join with adjacent capillaries, while at the surface they form capillary loops round the openings of the glands. Blood from the mucosal capillaries drains into venules, which take origin immediately beneath the surface epithelium (Fig. 1). Several of these venules join to form a single vertical mucosal vein, which terminates by entering one of the basal mucosal veins lying along the glandular surface of the muscularis mucosae. The basal mucosal veins form mutual anastomoses in varying degree, and each is

joined by several vertical mucosal veins. Blood finally passes from the basal mucosal veins into the veins of the submucosa, through communicating veins which pierce the muscularis mucosae. Occasionally a vertical mucosal vein passes through the muscularis mucosae without communicating with a basal mucosal vein.

Roth and Ivy (1945) have followed, by direct vision and histological sections, the processes leading to mucosal haemorrhage and the formation of erosions;

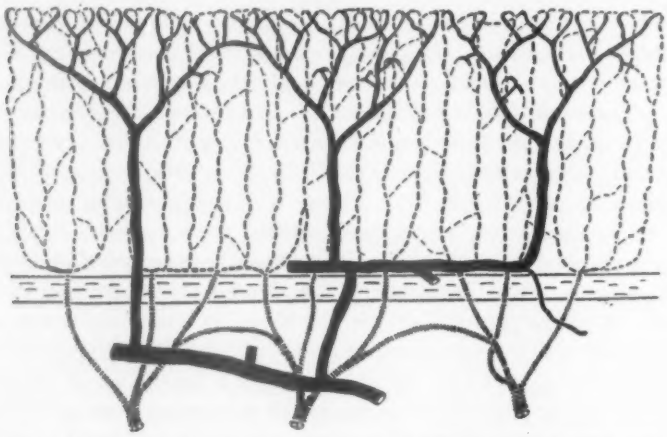

FIG. 1. Diagram of the vascular arrangement in the mucosa of the stomach (veins and venules, continuous lines; arteries and capillaries, interrupted lines). The branches of three mucosal arteries are seen piercing the muscularis mucosae. Three vertical mucosal veins and their tributaries are illustrated.

their observations were made in the stomach of the cat after the parenteral administration of caffeine and histamine. The first change observed was hyperaemia of the mucosa; this was followed by cyanosis, and during the transition stage the mucosa became swollen and succulent and the veins of the mucosa and submucosa were seen to be engorged. Scattered collections of red blood-cells and transudate were then found in the interstitial tissues, and when viewed from above they appeared as petechial or ecchymotic haemorrhages in the mucosa. In three to five hours, in the presence of highly acid gastric juice, these haemorrhagic areas were digested, leaving punched-out or ragged erosions. Wolf and Wolff (1947), from direct observation of the gastric mucosa of a human subject with a gastric fistula, found that certain emotionally charged situations were accompanied by severe and prolonged engorgement, with excessive secretion and motility of the stomach. In such a phase mucosal haemorrhages and erosions could be readily induced by even the slightest trauma, and minute mucosal haemorrhages often spontaneously succeeded vigorous contractions of the stomach wall. From a histological study of punctate haemorrhages of the gastric mucosa in human and in animal material, Hagemann (1909) concluded that the irregular-shaped haemorrhages occurring in the deeper layers of the

mucosa are caused by damage of the mucosal arteries and capillaries, whereas the more superficial cone-shaped haemorrhages result from damage to the mucosal veins and venules. Hagemann pointed out that the superficial haemorrhage begins immediately beneath the surface epithelium, at the site of origin of the venules, and when fully formed assumes the shape of a cone corresponding exactly to the region occupied by the tributaries and stem of a vertical mucosal vein. In five of the cases described above, in which death occurred within 24 hours of the onset of the acute illness, we were provided with an opportunity to reinvestigate the early vascular changes which occur in the gastric mucosa.

Methods. Our study is based on post-mortem material from Cases 2, 4, 5, 6, and 7. After fixation of the stomach in 10 per cent. formalin, frozen sections were cut at a thickness of 200 to 300 μ and stained by a modified Lepehne-Pickworth method (Campbell, Alexander, and Putnam, 1938). Although this staining method was described for the demonstration of the vascular pattern of the central nervous system, we have found that it also gives very satisfactory results when applied to the stomach. The principle of the method is that the red blood-corpuscles contained in the vessels are selectively stained by the application of the benzidine test for haemoglobin, while its advantage over the usual histological techniques lies in the fact that the thick sections permit the vascular tree and the areas of vascular disturbance to be seen as a morphological entity. In addition to the frozen sections, horizontal strips of mucosa were stained by the same method; these were obtained by separating the mucosa from the submucosa by means of a sharp blade and forceps. We were thus able to visualize the vascular disturbances in the mucosa in vertical and horizontal planes. Paraffin sections were also prepared, and these were stained with haematoxylin and eosin.

Histological findings. The predominant lesion in all our cases was the superficial mucosal haemorrhage. Haemorrhages into the deeper aspects of the mucosa also occurred, but were much less frequent; no areas of anaemic necrosis were observed. The earliest stage in the formation of a superficial haemorrhage was an aggregate of small perivascular collections of red blood-cells immediately beneath the surface epithelium. These small perivascular, and presumably diapedetic, haemorrhages increased in size, and eventually coalesced to form a typical wedge-shaped superficial haemorrhage; the surface epithelium overlying this lesion was always lost by the time the lesion was fully formed. By the Lepehne-Pickworth method it was clearly demonstrated that the superficial mucosal haemorrhage was of venous origin. Each group of small haemorrhages, which ultimately compose the fully developed lesion, was seen to occur in relation to the most superficial tributaries of a vertical mucosal vein (Plates 2 and 3, Figs. 6, 7, 8, and 10). The venules forming the source of these haemorrhages were often much dilated (Plate 3, Fig. 8). The veins of the mucosa and submucosa always showed some degree of congestion, and in the later stages, when the small haemorrhages had fused to form single lesions, the vertical and basal mucosal veins were especially engorged (Plate 3, Fig. 10). A greatly distended vertical mucosal vein thus formed the apex of each

superficial mucosal haemorrhage, the conical shape of the haemorrhage corresponding to the region occupied by the tributaries of the vein (Plate 3, Fig. 10). The haemorrhages in the deeper aspects of the mucosa were ill defined, and much smaller than those at the surface; they occurred in relation to the mucosal capillaries, close to their arterial origin. The capillaries themselves appeared normal. On a few occasions a small extravasation of erythrocytes was seen adjacent to one of the small venous channels passing obliquely through the circular muscle coat. The mucosal haemorrhages were unaccompanied by any cellular reaction.

In the later stages laking of the red cells and local destruction of the mucosa transformed the areas of mucosal haemorrhage into amorphous necrotic masses. The formation of erosions through digestion or sloughing of these necrotic masses was observed in cases in which their removal or separation was incomplete. Such lesions are termed haemorrhagic because of the necrotic, haemorrhagic debris which has remained adherent to their walls. Numerous non-haemorrhagic erosions were also observed, presumably having been formed by the clean separation or removal of haemorrhagic and necrotic areas. There is little doubt that the cause of the majority of the erosions was superficial mucosal haemorrhage and not the less frequent deep mucosal haemorrhage; the haemorrhages in the latter case were much smaller, and few had advanced to the stage of causing destruction of the mucosa. In most instances the erosions were funnel-shaped, and on a few occasions a vertical mucosal vein in the base of the lesion was closed by a thrombus. The fact that no venous thrombi were seen unless an erosion was present is strong presumptive evidence that the thrombosis is not primary but probably secondary to the exposure of the vessel to the gastric juice. No arterial thrombi were discovered in the numerous paraffin sections examined. In Case 6 several of the mucosal defects penetrated the muscularis mucosae, but none of these acute ulcers extended deeper than the submucosa. There was a scanty inflammatory-cell infiltration in the tissues immediately adjacent to the erosions and acute ulcers. In Cases 2 and 7, although bleeding had occurred into the lumen of the stomach, there was no microscopic evidence of any of the mucosal haemorrhages having reached the stage of erosion. In Case 5, in which the only macroscopic lesions were mucosal haemorrhages, a few haemorrhagic and non-haemorrhagic erosions were found on microscopic examination.

Discussion

Although erosions and acute ulcers of the upper digestive tract are always included in the differential diagnosis of haematemesis and melaena, the possibility of their association with intracranial disease is seldom considered in clinical practice. Gastrointestinal haemorrhage, occurring in organic brain disease and following neurosurgical operations, has been the subject of papers by Bodechtel (1935), Picard, Charbonnel, and Giraudet (1948), French, Porter, von Amerongen, and Raney (1952), Hoxsey (1953), and Davis, Wetzel, and Davis (1955). We consider that the occurrence of haematemesis or melaena in

cases of spontaneous intracranial haemorrhage is by no means rare, since seven cases of haemorrhage in the alimentary tract were observed by us within 13 months. Case 1 is of particular interest, because haematemesis was the presenting feature in a patient who was only subsequently found to have an intracranial lesion. A similar case was reported by Bodechtel (1935) of a man aged 35 years who was admitted to hospital because of haematemesis. He had complained of headache during the previous eight days, and was later found to have an intracranial lesion, a glioma of the right temporal lobe. The fact that haematemesis may be one of the presenting features in intracranial disease is illustrated further by the case reported by Laruelle and Reumont (1949) of a man aged 23 years, who developed sudden haematemesis and melaena, and died in coma a few days later. The intracranial disorder was a haemorrhagic tumour in the right frontal lobe, which proved to be a metastatic deposit from a testicular chorion-epithelioma. An analysis of the histories of these three cases shows that headache occurred either before or shortly after the haemorrhage. We suggest, therefore, that the presence of headache in these circumstances should direct attention to a possible neurogenic basis for the haematemesis.

All degrees of gastrointestinal haemorrhage have been reported in association with intracranial disorders. Davis, Wetzel, and Davis (1955) recorded 12 deaths from massive gastrointestinal haemorrhage following neurosurgical operations. Cases of fatal (Fisher, Watkins, Gardner, and Klotz, 1951) and nearly fatal (Globus and Ralston, 1951) gastroduodenal haemorrhage have occurred in children within a few days of successful intracranial operations. In a child with meningococcal meningitis, who suddenly collapsed and died 12 days after the onset of the illness, the cause of death was found to be haemorrhage from an acute duodenal ulcer (Hartung and Warkany, 1938). An example has been described of severe gastrointestinal haemorrhage, requiring blood transfusion, three days after a head injury (Ask-Upmark, 1939). Severe bleeding from the digestive tract developed in a woman 15 days after cerebral infarction; operation revealed four acute gastric ulcers high up in the lesser curvature (Sarason and Levy, 1954). Finally, Baker, Brown, and Cornwell (1952) recorded seven cases of severe gastric haemorrhage complicating bulbar poliomyelitis. In four of these cases, in which the patients had appeared to be progressing satisfactorily, the first indication of the bleeding was the sudden appearance of shock; two of these patients died within a few hours, and the correct cause of the sudden deterioration was apparent only at autopsy; in the other two patients vomiting of blood indicated the correct diagnosis, and measures to combat the loss of blood were instituted. The authors emphasized the importance of early recognition and treatment of gastric haemorrhage in bulbar poliomyelitis, pointing out that it may constitute a medical emergency which should be watched for in all cases. We suggest that this dictum be extended to include all forms of acute intracranial disturbance, since the examples we have quoted above indicate that severe gastrointestinal haemorrhage may complicate a wide variety of such disorders.

Rapid healing is the natural course of erosions and acute ulcers of the stomach,

and there is no evidence that such lesions do not follow a similar course when associated with intracranial disease. In Case 1, in which the stomach was examined on the sixth day after the haematemesis, the widespread focal damage to the mucosa was only discovered on microscopic examination, and in Case 3 radiological examination of the stomach and duodenum one month after the onset of the haematemesis revealed no evidence of ulceration.

Although chronic peptic ulcer and intracranial disease are occasionally found to coexist, most authors consider that there is no aetiological relationship between the two conditions. From an analysis of 2,437 autopsies performed in Zurich in 1947 and 1948, Betz (1949) found the combination of intracranial lesions and chronic peptic ulcer to be no greater than the calculated chance association. Sack (1946) made a clinical and radiological study of the upper digestive tract in 100 patients who had sustained brain damage as a result of head injuries; these patients were examined six to 24 months after the injury, and in only one instance was there evidence of chronic peptic ulceration. A similar series of cases was reported by Kalk (1946–7): 342 patients were examined radiologically and gastroscopically 17 to 40 months after brain injury, and chronic peptic ulceration was found in only five cases. The ulcer was known to have been present before the injury in three of these five cases. In a series of 512 cases of pituitary tumour, Wilson, Olson, and Rivers (1946) discovered only five (one per cent.) associated with peptic ulcer. Ivy, Grossman, and Bachrach (1950), after a review of the literature dealing with experimental production of ulcers, reached the conclusion that no acceptable evidence had yet been presented to show that chronic peptic ulcer results from a lesion of the brain.

The generally accepted theory that the acute gastrointestinal lesions associated with intracranial disease are due primarily to vascular disturbances in the mucosa is strongly supported by the histological findings of our cases. The cause of the local vascular disturbance has been disputed. Schiff (1846, 1867) considered the primary disorder to be dilatation and stasis of the blood-vessels arising as a consequence of vasomotor paralysis. Others (Beneke, 1908; Hart, 1919) have regarded prolonged vasoconstriction as the essential underlying factor, while a third hypothesis (Nicolaysen, 1920; Cushing, 1932) attributes the vascular disturbance to compression of arteries and veins by spasmodic contractions of the gastric musculature. The recent demonstration in the human stomach of arteriovenous anastomoses in the submucosa, capable of short-circuiting the mucosal arteries directly into the veins (Barlow, Bentley, and Walder, 1951), introduces yet another possible mechanism. Venous dilatation and perivascular haemorrhages were observed in all our histological material. This picture, well shown by the Lepehne-Pickworth method, appears to be characteristic of partial or complete stasis (Campbell, Alexander, and Putnam, 1938). It is not possible to determine whether the stasis resulted from vasomotor paralysis, venous compression, or transient ischaemia of the mucosa due to one of the mechanisms already mentioned. Whatever the precipitating factor, there can be no doubt that the associated venous dilatation and perivascular haemorrhages are of great importance in the train of events leading to erosion

and the formation of acute ulcers. We have confirmed Hagemann's observations that the small perivascular mucosal haemorrhages, situated immediately beneath the surface epithelium, occur in relation to the tributaries of a vertical mucosal vein, and that these minor haemorrhages eventually coalesce to form a typical wedge-shaped superficial mucosal haemorrhage. The superficial mucosal haemorrhage, which was the predominant lesion in our cases, is followed by necrosis, and sloughing or digestion of the necrotic area leads to the formation of the mucosal defects.

The recognized efferent pathways through which the central nervous system acts on the stomach are the connexions of the autonomic nervous system and the pituitary-adrenal axis; controlling centres of both these systems are situated in the hypothalamus. In Cases 2, 6, and 7 there was damage to the hypothalamus, while in Case 4 the intracranial haemorrhage was in a position to interfere with its centripetal connexions with the frontal lobe, and in Case 5 with its centrifugal fibres in the brain-stem. In Case 1 the localization of the large amount of blood-clot at the base of the brain may have resulted in hypothalamic disturbance, and in Case 3 it is possible that the transient hyperglycaemia was a manifestation of hypothalamic upset. We should like to point out that intracranial lesions which involve the hypothalamus are not always associated with lesions of the digestive tract, which occur only in a minority of cases. Furthermore, mucosal erosions and acute ulcers may be associated with intracranial lesions which do not involve the hypothalamus or its known fibre connexions (Globus and Ralston, 1951; French, Porter, von Amerongen, and Raney, 1952; Davis, Wetzel, and Davis, 1955). Activity of the autonomic nervous system has been shown by Wall and Davis (1951) to be influenced by three separate cerebral cortical systems; only one of these, which arises in the frontal lobe, passes through the hypothalamus; the others arise from the sensorimotor cortex and the temporal lobe respectively, and do not traverse the hypothalamus. The existence of these latter two systems implies that absence of hypothalamic involvement does not exclude involvement of the autonomic nervous system. In spite of considerable experimental work, the role of the autonomic nervous system in the production of the acute gastrointestinal lesions is still not clear. Cushing (1932) considered the primary disturbance to be one of parasympathetic overactivity. He suggested that intracranial lesions might stimulate the parasympathetic centre in the hypothalamus, or the fibres therefrom as they descend in the brain-stem. Alternatively the lesion might paralyse the antagonistic sympathetic fibres, causing a functional release of the vagal system. On the other hand Watts and Fulton (1935) suggested that the gastrointestinal lesions, which they produced in monkeys by means of hypothalamic lesions, were due to a release or irritation of the sympathetic nervous system. Each of these hypotheses, attributing the lesions of the alimentary tract to the overactivity of one or other component of the autonomic system, has received support from other investigators; the experimental evidence on which the support is based has been the subject of reviews by Sheehan (1940) and Ivy, Grossman, and Bachrach (1950).

There was severe brain damage in five of the seven cases reported in the present paper. It has been observed, in experimental lesions of the interbrain (Sheehan, 1940), that the severity of the intracranial lesion appears to influence the frequency of production of gastroduodenal lesions, the large destructive injuries being those most likely to provoke gastrointestinal haemorrhages and erosions. In man, also, there appears to be little doubt that the severity of the intracranial lesions is a factor in the production of acute lesions of the alimentary tract, although its precise importance is difficult to assess. Since, in the great majority of reported cases, the diagnosis of the lesions in the digestive tract has been made at autopsy, the severe and fatal forms of intracranial lesion naturally predominate. In patients with less severe, non-fatal intracranial lesions, there is the possibility of acute gastrointestinal lesions which remain clinically silent and so pass unrecognized. Knowledge of the incidence of acute lesions of the digestive tract in non-fatal forms of intracranial disease would be of practical value in assessing the risks of anticoagulant therapy, which is at present undergoing trial in certain forms of cerebral vascular disease (Wright and McDevitt, 1954).

It has long been known that mucosal erosions, acute ulcers, and perforations of the gastrointestinal tract may occur in association with a wide variety of acute pathological processes other than those of the central nervous system, and also in the terminal stages of many chronic diseases. In 1825 Desbarreaux-Bernard described several examples of spontaneous perforation of the stomach in patients who died after surgical operations, burns, and compound fractures. Acute peptic ulceration following burns was originally reported by Swan (1823), and Curling (1842) was the first to emphasize the frequency with which the two conditions are related. It is of interest that changes in the brain, consisting of oedema, degeneration of ganglion-cells, and demyelination, have been described in cases of death after extensive burns (Globus and Bender, 1936; Walker and Shenkin, 1945; Madow and Alpers, 1954). As far back as 1867 Billroth described a case of acute duodenal ulceration following a surgical operation, and in 1899 von Eiselsberg reported a series of eight cases of gastric and duodenal haemorrhage after operation. Mucosal erosions and acute ulcers of the gastrointestinal tract have been described in association with many other conditions, including acute inflammatory disease (Perry and Shaw, 1894; Hurst and Stewart, 1929), acute myocardial infarction (Globus and Ralston, 1951; Mears, 1953; Fletcher and Harkins, 1954), and fractures (Wangensteen, 1945; Mears, 1953). Several hypotheses have been advanced to provide a common aetiological basis for the gastrointestinal lesions found with these diverse conditions. Desbarreaux-Bernard (1825) considered that the severe pain resulting from surgical operations or burns was the causal factor in his cases of spontaneous perforation of the stomach, but did not speculate on the mechanism involved. In animal experiments Ebstein (1874) found that stimulation of a peripheral nerve containing pain-fibres readily produced haemorrhages and erosions in the gastric mucosa. He was able to produce similar lesions by asphyxiating processes, injections of strychnine, lesions of the central nervous system, and damage to the internal

ear, and attributed the mucosal haemorrhages to the rise in blood-pressure which accompanied these procedures. Penner and Bernheim (1939) pointed out that shock, characterized by a decrease in the circulating blood-volume, is of frequent occurrence in the wide variety of pathological conditions described above. They attributed the mucosal damage to the increased capillary permeability resulting from stasis, the latter being a consequence of arteriolar constriction arising in response to shock. Selye (1946) has shown that gastrointestinal ulceration occurs in animals during the shock phase of the alarm reaction. Among other authors, Aschoff (1924) held the view that vomiting was a factor of importance in the aetiology of haemorrhagic erosions; he considered that venous stasis and mucosal haemorrhages result from compression of arteries and veins produced by the strong contractions of the gastric musculature which occur during the act of vomiting.

Considerable attention has recently been directed to the possibility of an increased secretion of corticotrophin as the basis of gastric erosions and acute ulcers found in association with so many different disorders (McDonnell and McCloskey, 1953; Fletcher and Harkins, 1954). After the administration of corticotrophin or cortisone there is an increase in the gastric secretion of acid and pepsin, unaltered by vagotomy or ganglion-blocking agents, and a similar increase in acid and pepsin secretion follows surgical operations (Gray, Ramsey, Reifenstein, and Benson, 1953). Surgical operations are found to raise the plasma levels of 17-hydroxycorticosteroids (Frankson, Gemzell, and von Euler, 1954) and increase the urinary excretion of corticosteroids (Thorn, Jenkins, and Laidlaw, 1953). Similar increases in plasma steroid levels are commonly observed in painful conditions, and also at the time of death (Bayliss, 1955). Moreover, in many medical diseases there is an increased output of urinary corticosteroids (Cope, Boysen, and McCrae, 1951). Hume (1949) has demonstrated in dogs that lesions placed in certain areas of the anterior hypothalamus abolish the usual eosinopenic response to such stress-provoking stimuli as trauma, chemical irritants, and injections of adrenaline and insulin. Porter (1953) has brought together three lines of evidence which support participation of the hypothalamus in the pituitary-adrenal response. Using the cat as the experimental animal, he observed that the administration of various stress-producing agents increased the electrical activity of the posterior hypothalamus; after destruction of the posterior hypothalamus stress stimuli failed to induce an eosinopenia, whereas in normal animals electrical stimulation of the posterior hypothalamus produced an eosinopenia. In animals subjected to the stress of trauma it has further been shown (Hume, 1953) that nerve impulses from the injured area are essential for the initiation of the hypothalamic-pituitary-adrenal response. If the area of trauma has been denervated there is no evidence of increased corticotrophin secretion. The hypothesis that increased adrenocortical activity is of aetiological significance in peptic ulceration is supported clinically by several reports of the occurrence of acute ulcers, and the exacerbation of chronic ulcers, in patients receiving corticotrophin or cortisone (Gray, Benson, Reifenstein, and Spiro, 1951; Davis and Zeller, 1952; Forbes,

1952). It has been demonstrated in animals (Selye, 1946) that stimulation of the pituitary-adrenal mechanism is not essential for the production of acute gastrointestinal ulceration; the lesions of the digestive tract which occur during the alarm reaction are not prevented by hypophysectomy or adrenalectomy; indeed, they tend to be more severe in the absence of either or both of these glands. Selye (1951) presumed that these acute ulcers are largely due to the intense autonomic discharge which occurs during exposure to stress and elicits marked peristaltic, vasomotor, and secretory reactions in the gastrointestinal tract. The effect of cortisone on the blood-vessels of the stomach is at present unknown, and no satisfactory evidence has yet been presented to show that cortisone is capable of producing the early vascular lesions in the mucosa which we have described above. Whatever the causal factors in the production of these early vascular disturbances may be, it appears highly probable that the resulting mucosal damage will be further aggravated by any increase in the output of a substance, such as cortisone, which is known to increase the secretion of acid and pepsin.

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Summary

Seven cases are described of gastrointestinal haemorrhage occurring in association with a cerebro-vascular accident. In five instances the intracranial lesion was a cerebral haemorrhage, and in two it was a subarachnoid haemorrhage. Haematemesis occurred in five cases, and melaena in one; in the seventh case no clinical evidence of bleeding was obtained, but blood was found in the stomach at autopsy.

In the five cases of cerebral haemorrhage death occurred within 24 hours of the onset. At autopsy the outstanding feature in the digestive tract in each of these cases was the presence of numerous punctate haemorrhages and ecchymoses in the mucosa of the stomach. There were also erosions in two cases, and erosions and small acute ulcers in one.

A histological study was made of the early lesions in the gastric mucosa. With the benzidine stain (Lepehne-Pickworth method), described for the demonstration of the vascular pattern of the central nervous system, areas of vascular disturbance in the stomach were clearly outlined. The predominant lesion was found to be a wedge-shaped haemorrhage situated superficially in the gastric mucosa. The observation of Hagemann (1909) that this superficial mucosal haemorrhage is of venous origin, and owes its characteristic shape to the anatomical arrangement of the mucosal venules, has been confirmed. The superficial haemorrhage is followed by local necrosis of the mucosa, and digestion or sloughing of the necrotic area leads to the formation of an erosion or, if the muscularis mucosae is penetrated, an acute ulcer.

Haematemesis was the presenting feature in one of the two cases of subarachnoid haemorrhage. This patient died six days after the onset of the illness; at necropsy the stomach appeared normal, but microscopic examination revealed evidence of widespread focal mucosal damage. The other patient with subarachnoid haemorrhage survived, and radiological examination of the upper gastrointestinal tract one month after the onset of the haematemesis gave a negative result.

The pathogenesis of acute gastrointestinal lesions associated with intracranial disease is discussed.

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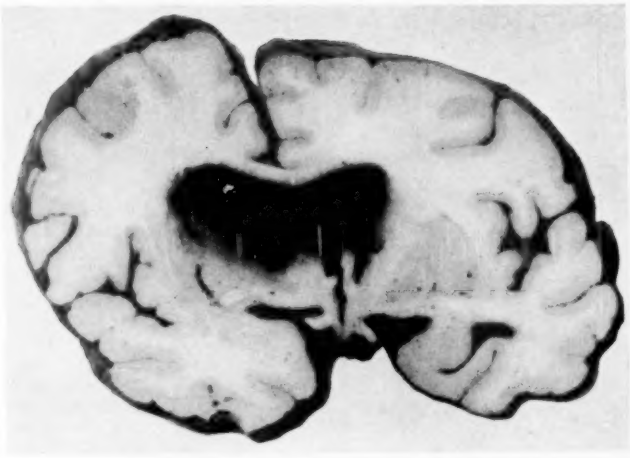

FIG. 2. Case 4. Brain, coronal section showing haemorrhage involving right corpus striatum and lateral ventricles

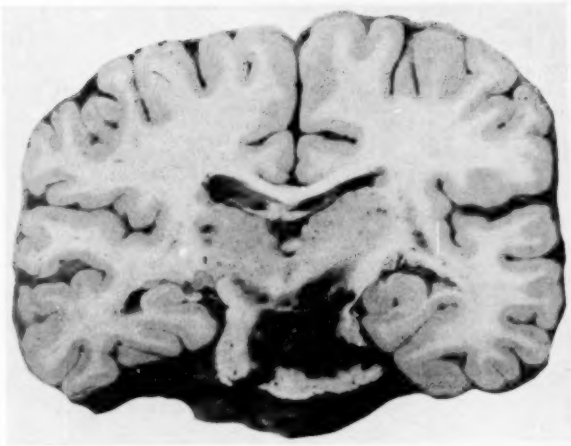

FIG. 3. Case 5. Brain, coronal section showing pontine haemorrhage with extension into the mid-brain

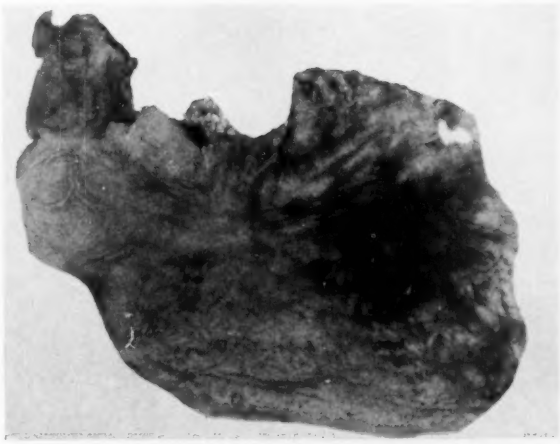

FIG. 4. Case 2. Stomach and first part of duodenum showing distribution of the mucosal haemorrhages

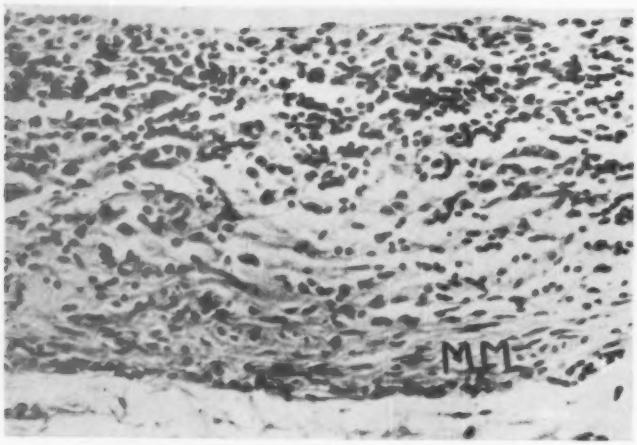

FIG. 5. Case 1. Stomach, showing early repair of an area of mucosal damage. MM = muscularis mucosae (haematoxylin and eosin, ×250)

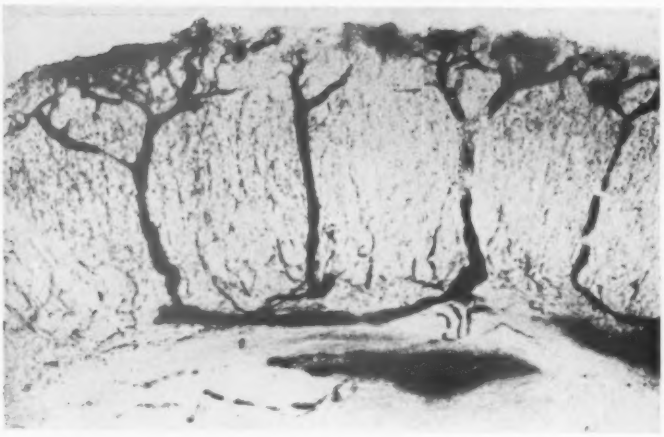

FIG. 6. Case 2. Stomach. Early stage in the formation of superficial mucosal haemorrhages, with small extravasations occurring in relation to the surface venules (benzidine stain, ×50)

FIG. 7. Case 2. Gastric mucosa showing the appearance of lesions, similar to those in Fig. 6, in horizontal plane (benzidine stain, ×40)

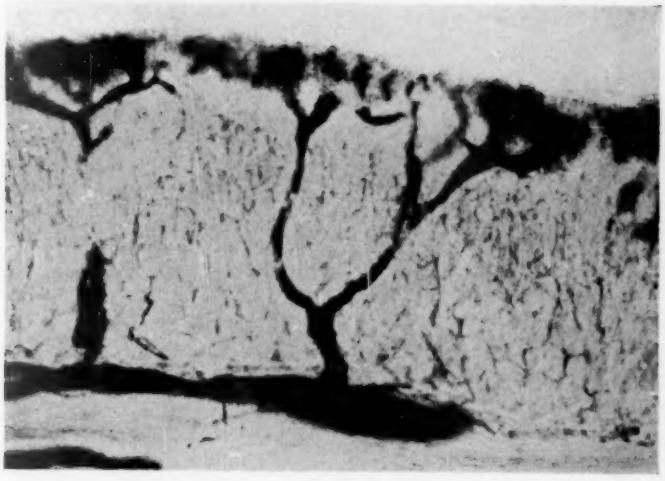

FIG. 8. Case 5. Gastric mucosa showing perivascular haemorrhages in relation to dilated venules (benzidine stain, ×60)

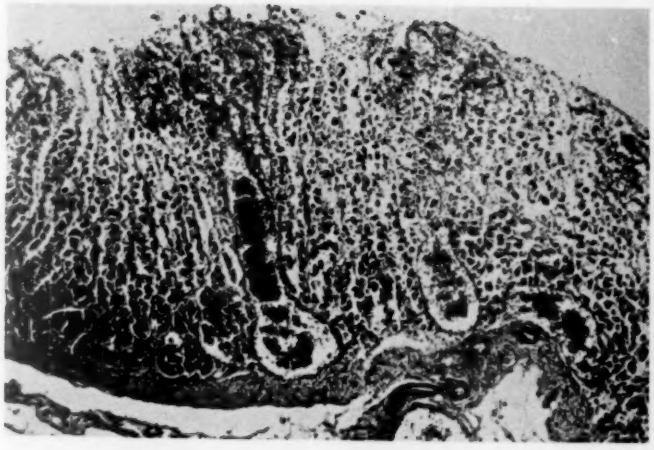

FIG. 9. Case 4. Gastric mucosa, showing dilated vertical mucosal vein and superficial haemorrhage (haematoxylin and eosin, ×70)

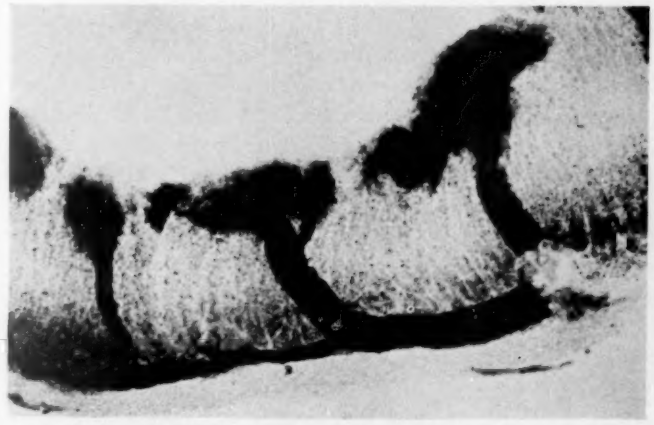

FIG. 10. Case 4. Stomach. Fully developed wedge-shaped superficial mucosal haemorrhages and marked engorgement of the vertical and basal mucosal veins (benzidine stain, ×55)

616.61–008.822.32

POTASSIUM-LOSING RENAL DISEASE[1]

Renal and Metabolic Observations on a Patient Sustaining Renal Wastage of Potassium

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With Plate 4

The frequency with which chronic renal disease is complicated by potassium depletion is unknown, and when potassium deficiency does arise it may be difficult to detect its effects among the many clinical and biochemical disturbances of renal failure. Low serum levels of potassium, in themselves sufficient to suggest potassium deficiency, may be seen not infrequently in renal disease if assiduously sought (Hamburger, Crosnier, Funck-Brentano, Rapin, and Masson, 1954), but the finding of normal or elevated levels does not preclude the possibility of depletion. Moore, Edelman, Olney, James, Brooks, and Wilson (1954), measuring the exchangeable body-potassium with ^{42}K in patients with renal disease, have found that the loss of one-third, or more, of body-potassium may be compatible with serum-potassium levels as high as 8 mEq. per litre. It is evident that the loss of such large amounts of the principal intracellular cation could give rise to functional disturbances, and that these might contribute to the clinical picture of renal insufficiency. General clinical opinion inclines to the belief that moderate depletion of potassium produces no significant clinical effects. That this may be true of small losses is indicated by the experimental study of Black and Milne (1952), whose subjects suffered no clinical symptoms when depleted of rather less than 10 per cent. of body-potassium. On the other hand, when experimentally depleted of almost 30 per cent. of body-potassium, the subjects of Fourman (1954) experienced a variety of unpleasant symptoms. Among these anorexia, apathy, muscular weakness, and severe thirst not relieved by drinking are often experienced by patients with renal insufficiency; and their occurrence in this circumstance is not always easily explained. Doubtless a severe depletion of sodium is sometimes responsible for similar symptoms in renal disease, and the beneficial effects of sodium restitution are well known. When the possibility of potassium deficiency arises in patients with advanced renal disease, the problem can rarely be investigated objectively as in the experimental studies cited above; and the hazard attending potassium administration in the presence of renal excretory failure may render inadvisable the giving of potassium salts as a therapeutic test.

The present communication describes the detailed investigation of a single

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patient who, from a combination of anorexia and renal insufficiency, became depleted of about one-half her total body-potassium. It was possible, because of the exceptional co-operation of the patient and the absence of danger attending investigation, to examine aspects of the clinical problem of renal disease and potassium deficiency in unprecedented detail. In consequence we are able to comment both on the renal mechanisms responsible for potassium wastage and on the metabolic effects of severe potassium depletion. It is intended to apply the results of this study to the interpretation of problems presented by other patients, in whom potassium wastage occurs through the kidneys, in a general review of potassium deficiency and renal disease (Stanbury and Mahler, 1956). This first paper is concerned equally with the morbid physiology of potassium depletion and the clinical problem of 'potassium-losing renal disease'.

Case Report

A. F., a 63-year-old housewife, was first admitted to a medical ward on March 29, 1954, complaining of thirst and profound muscular weakness. Six weeks earlier she had developed a typical attack of cholecystitis, and cholecystography on March 24, when she was an out-patient, failed to outline the gall-bladder. On frequent occasions during the previous 10 years she had experienced attacks of right subcostal pain associated with anorexia and occasional vomiting; in some of these attacks the urine became dark and the stools were pale. For at least five years there had been nocturnal frequency of micturition, urine being passed once or twice each night. She sometimes had scalding pain on micturition, and considered that both this symptom and the nocturia were more noticeable during an attack of cholecystitis. There was no history of previous recognized renal disease, and her two pregnancies had been uncomplicated. For a year she had been unduly thirsty, but this symptom was not troublesome until six weeks before admission. Then, with the onset of cholecystitis, she lost her appetite, and within a few days thirst became compulsive. The tongue and lips became dry, cracked, and painful, and, despite almost constant drinking of water, she was unable to control her thirst. Presumably as a consequence of the increased intake of fluid, she developed an inconvenient diurnal frequency of micturition, and needed to get up four or five times at night. Because of her anorexia, sore mouth, and abdominal discomfort, she ate little food in the next six weeks, and lost about 14 lb. in weight. She could not date precisely the onset of her muscular symptoms, being unable to distinguish between a general weariness and actual loss of muscle strength. About 10 days before admission to hospital she developed muscular aching in the thighs and upper arms, and the limbs felt heavy and clumsy. When she attended for cholecystography she found it difficult to lift her feet up a single step, and could barely walk. She returned home to bed, and soon found herself unable to sit up, raise her legs, or even move one leg over the other. She could not raise her arms to brush her hair, or safely hold a cup. Speech, deglutition, and respiration were unaffected; but she noticed breathlessness with her unavailing attempts to move her trunk or legs. When her muscles began to ache she had experienced transitory tingling in the hands; but otherwise she has never had any symptoms that could possibly be construed as tetanic, and no objective evidence of tetany has been found.

On admission to hospital the patient was unable to move in bed, and could do nothing for herself. It is of some interest that the house physician tended to

regard this disability as hysterical, and the nurses were convinced that she was 'not trying'. The lips were dry and cracked, and the tongue red, dry, fissured, and bleeding in places. The skin was dry and inelastic. The pulse was regular at 80 per minute, and the blood-pressure 110/80. There was minimal, but clinically obvious, hyperpnoea when she was at rest, the respiratory rate varying between 20 and 26 per minute. The heart and lungs were normal. There was tenderness on deep palpation over the gall-bladder. All tested movements were conspicuously weak, but examination was insufficiently critical to detect differential involvement of separate muscle-groups. The knee- and biceps-reflexes were absent, and there was just perceptible activity of the other deep limb-reflexes; the abdominal reflexes were absent, and the plantar reflexes normal. The muscles of the upper limbs, and both quadriceps femoris muscles, were tender on pressure. There were no objective sensory abnormalities; the Trousseau test for latent tetany was negative. The bones were not tender. Proteinuria was found on routine testing, but there was no glycosuria. The serum-potassium level on the day of admission was 2·6 mEq. per litre, and the serum-sodium 138 mEq. per litre; the blood-urea was 24 mg. per 100 ml. The serum-chloride level was 102 mEq. per litre and, despite the clinical evidence of desiccation, the chloride concentration in a casual urine specimen was 63 mEq. per litre. Two days later the serum-potassium level had fallen to 1·8 mEq. per litre, and treatment with alkaline potassium salts was started. After four days she had received about 250 mEq. of potassium, and the serum-potassium level was 2·05 mEq. per litre. She was then transferred to our care for investigation and treatment.

Further examination revealed nothing of much significance. The muscle weakness appeared to be generalized, and it was now possible to elicit with difficulty all the deep limb-reflexes. She was able to sit up unaided and comb her hair. In the absence of symptoms suggestive of steatorrhoea, the finding of proteinuria and the history of nocturia and dysuria made the most likely diagnosis potassium deficiency from renal loss, with chronic pyelonephritis the probable cause. It was realized that a long period of reduced feeding must have contributed to the potassium depletion. The patient was fully reassured as to early complete recovery from her frightening muscular symptoms, and she agreed to co-operate in a full metabolic study. She was allowed to choose a diet of her own liking, and adhered to it strictly throughout the period of study. The diet contained no added salt. During the first week of observation she took the diet without any supplement, while a variety of investigations was carried out; replenishment was then started with supplementary potassium salts by mouth. Initially she was given 10 gm. (134 mEq.) daily of KCl, but on the second day she had pyrexia (101° to 102° F.), and her tachypnoea increased. This febrile episode was associated with dysuria, pyuria, and a coliform infection of the urine, but it was felt that hyperchloraemic acidosis (serum chloride 108 mEq. per litre), resulting from the administration of KCl, could be contributing to the respiratory disturbance. Potassium replenishment was accordingly continued with $KHCO_3$ in an equivalent dose, and this supplement was given for the next 13 days (see page 25, Fig. 1). The urinary-tract infection responded to treatment with streptomycin, and we were unable to decide whether pyrexia or acidosis was responsible for the hyperpnoea. From the 16th to the 21st day of replenishment $KHCO_3$ was replaced by KCl, but no hypernoea accompanied the resulting hyperchloraemia (Fig. 1). After 21 days of treatment potassium administration was stopped; it was resumed, in a dose of 6 gm. (60 mEq.) $KHCO_3$ daily, when she developed a typical attack of cholecystitis on May 20. The cholecystitis responded quickly to streptomycin therapy. She was

discharged from hospital on June 3, with a serum-potassium level of 4 mEq. per litre, and receiving the same dose of $KHCO_3$.

Potassium replenishment produced certain well-defined clinical changes. There was the anticipated subjective and objective increase in muscle power. An equally impressive change was the rapid alleviation of thirst, and the fact that the clinical signs of desiccation disappeared slowly without administration of any sodium chloride other than the 56 mEq. Na and 63 mEq. Cl ($\equiv$3·5 gm. NaCl) present in her daily diet. By the end of the third week she had gained 4 kg. (8·8 lb.) in weight; skin turgor, and the appearance of her lips and mouth, were normal. The arterial blood-pressure remained essentially unchanged.

Most of the investigations to be described were carried out during her first stay in hospital. The patient was twice subsequently admitted for the purpose of cholecystectomy, which was ultimately performed by Mr. R. P. Jepson on August 24, 1954. On each admission the patient received a constant diet, and additional, if incomplete, metabolic observations were made. The results of the later investigations will not be described in detail, but relevant parts of them will be mentioned in the course of discussion. At operation a chronically infected gall-bladder, containing many facetted stones, was removed. Specimens of muscle, rib, liver, and a minute renal biopsy were obtained for the purposes of diagnosis and chemical analysis. The kidneys and pancreas appeared normal on palpation, and on inspection so far as this was possible. The liver was abnormally firm and finely granular; histological examination revealed an active cholangitis, with early fibrotic changes in the portal tracts. None of the tissues taken showed evidence of amyloid deposit or myelomatosis. There were no complications in the period immediately following operation, and the patient was ambulant when, on the 14th day, she developed a sore throat and cough. The temperature rose to 101° F., and she was found to have a right lower lobar pneumonia, which was treated with penicillin. During the same evening she began to vomit effortlessly and repeatedly, and no bowel sounds could be heard on auscultation of the abdomen. The blood-pressure fell to 75/50, and the patient was giddy on sitting up in bed; she was complaining of thirst, and there was hyperpneoa. The blood-urea had risen to 72 mg. per 100 ml., and the serum-electrolyte levels were as follows: K, 2·6 mEq. per litre; Na, 130 mEq. per litre; Cl, 96 mEq. per litre; CO_2, 27 mM. per litre. She was given a rapid infusion of one litre of Ringer's solution, to which noradrenaline was added. Subsequently, in a period of about 12 hours, she received 1·5 litres of a solution containing sodium chloride 120 mEq. and potassium lactate 30 mEq. per litre. This infusion was supplemented with a mixture of alkaline potassium salts by mouth. The blood-pressure was rapidly restored, and after a few uncomfortable days recovery was uneventful. A week after the onset of ileus the blood-urea level was 26 mg. per 100 ml. The patient has been under supervision for a further nine months, and has remained well. We have not felt justified in withdrawing the potassium supplement without metabolic control in hospital. Consequently she has continued to take 6 gm. (60 mEq.) $KHCO_3$ daily by mouth, and with this treatment her serum-electrolyte levels have remained within normal limits.

Routine Investigation

Blood changes. At the commencement of the metabolic study the serum-electrolyte levels were as follows: K, 2·4 mEq. per litre; Na, 136 mEq. per litre; Cl, 98 mEq. per litre; CO_2, 26 mM. per litre; inorganic phosphorus, 1·24 mg. per 100 ml. Subsequently about 30 specimens of blood were examined, and

results of these examinations are incorporated in Figs. 1, 2, 3, 4, and 5. The following salient features call for particular comment.

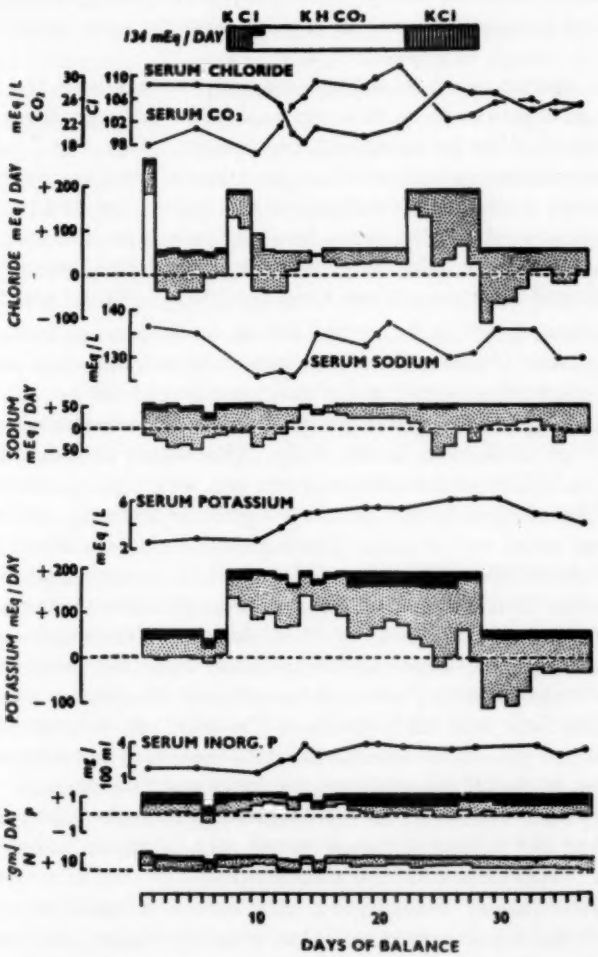

FIG. 1. Metabolic balances and changes in serum-electrolyte levels during potassium replenishment.

In the charting of balance data, intake is indicated by the height of the columns above the interrupted base-line; faecal (black) and urinary (stippled) outputs are plotted sequentially downwards from the intake line. A *positive* balance is represented by an enclosed white area *above*, a *negative* balance by a stippled area *below*, the base-line. Serum changes are charted immediately above the appropriate block of balance data.

1. Initially the serum-chloride and serum-bicarbonate levels were normal. Thus, although blood pH measurements were not made, there was no evidence of metabolic acidosis. A large dose of ammonium chloride (11 gm.),

given for diagnostic purposes, produced a hyperchloraemic acidosis (serum-chloride 108 mEq. per litre, bicarbonate 18 mEq. per litre), from which the patient recovered slowly. Subsequently she was hyperchloraemic when receiving KCl, and normal or slightly alkalotic when receiving $KHCO_3$ (Fig. 1).

2. The serum-potassium level increased progressively with the cumulative retention of potassium, until serum levels of 6·3 mEq. per litre necessitated withdrawal of the potassium-salt supplement. (Figs. 1 and 5.)
3. The conspicuous hypophosphataemia corrected itself spontaneously, with no treatment other than consumption of a normal diet and administration of potassium salts. The serum levels of potassium and inorganic phosphorus increased roughly in parallel, until the latter became stable at a normal level of between 3 and 4 mg. per 100 ml. (Figs. 1 and 5.)

The blood-urea level was 24 mg. per 100 ml. at the start and 30 mg. per 100 ml. on completion of potassium replenishment. Serum apparent creatinine remained constant at between 1·0 mg. and 1·1 mg. per 100 ml. There was no anaemia, haemoglobin being 14·8 gm. per 100 ml. on commencement and 12·7 gm. per 100 ml. at the end of the study. The white-cell count was normal. There was marked hyperglobulinaemia (4·9 gm. to 5·7 gm. per 100 ml.), with diminished serum-albumin (2·8 gm. to 3·3 gm. per 100 ml.), and the thymol turbidity was raised to 7·8 units. Electrophoretic analysis of the serum (Dr. L. Golberg) showed that the excess of globulin was due to a fraction migrating somewhat more slowly than the usual gamma-globulin (?$gamma_2$, ?delta). These findings raised the possibility of myelomatosis, for which there was no other clinical evidence. Bone-marrow obtained when the patient was anaesthetized for cholecystectomy revealed no evidence of myeloma cells, although normal plasma cells were fairly frequent (Dr. M. C. G. Israëls). The protein changes have not reverted to normal during 15 months of surveillance; we have ascribed them to the effects of chronic infection and liver damage.

Alimentary-tract investigation. Steatorrhoea was excluded by fat-balance determination; the patient absorbed 95 per cent. of fat on a diet containing 60 gm. of fat. There was complete achlorhydria.

Skeletal investigation. Radiological examination revealed no evidence of osteomalacia; the bones were of normal radiological density, and there were no Looser's nodes. The serum-calcium level remained between 9·5 and 9·8 mg. per 100 ml. and, except in attacks of cholecystitis, the serum-alkaline-phosphatase level was normal (5 to 9 King–Armstrong units per 100 ml.). Bone obtained at the time of operation was histologically normal (Professor A. C. P. Campbell).

Studies of Renal Function

1. *Proteinuria; aminoacid excretion.* Proteinuria was always minimal, and occasionally absent, on routine testing. Electrophoretic analysis of a concentrated specimen revealed all the protein fractions present in simultaneously sampled plasma; albumin and the slowly migrating globulin were preponderant.

This protein leak suggested a glomerular lesion. Excretion of aminoacid-nitrogen was within normal limits. Reducing substances were not detected in the urine, even during glucose-tolerance tests.

2. *Excretion pyelography.* There was no nephrocalcinosis, and the renal pelves were outlined normally. There was thus no evidence of significant interference with the tubular transport of diodrast. (This examination was made one week after starting potassium replenishment.)

3. *Capacity for urine concentration and dilution.* When she was depleted of potassium, the patient's extreme thirst made fluid deprivation unjustifiable; accordingly the kidneys were not specifically challenged to produce a concentrated urine. No urine specimen was of higher specific gravity than 1,010. (The possible effects of potassium replenishment on urine-concentrating capacity are discussed subsequently.) Urine with specific gravity of 1,001 to 1,000 was produced after a normal latent period following ingestion of a water load, and the equivalent quantity of water was excreted in normal time.

4. *Nocturia and the diurnal excretory rhythm.* Nocturia appeared to be due to a complete inversion of the normal diurnal excretory rhythm for sodium and chloride (Stanbury and Thomson, 1951); at midnight the rate of excretion of water, sodium, and chloride was twice as great as at midday. There was no evidence of the customary diurnal rhythm in potassium and hydrion excretion (Mills and Stanbury, 1954).

5. *Capacity for urine acidification.* As a stimulus to urine acidification, 206 mEq. (11 gm.) of ammonium chloride was given orally over a six-hour period. The plasma-bicarbonate level fell to 18 mM. per litre, but in spite of this gross acidosis the lowest subsequent urine pH was 6·48. Bicarbonate excretion continued at about 5 μEq. per minute, and the rate of ammonia excretion was never greater than 20 μEq. per minute. The effects of the dose of ammonium chloride on the excretion of sodium, chloride, and potassium are shown in Table I (page 33). Tests for urine acidification were repeated twice at intervals up to six months after potassium replenishment, and a urine pH no lower than 6·4 was obtained on each occasion. On these two occasions the test was followed by administration of 250 mg. of the previously unavailable carbonic-anhydrase inhibitor acetazoleamide ('diamox'). This increased the urine pH from about 6·4 to about 7·6, and bicarbonate excretion increased from about 30 μEq. to 110 μEq. per minute.

6. *Renal clearances.* Before potassium replenishment, renal clearances were determined by standard techniques using short urine-collection periods:

Endogenous 'creatinine' (C_{cr})	62 ml. per minute.
Inulin (C_{in} or glomerular filtration rate)	61 ml. per minute.
Potassium (C_K)	14 ml. per minute.
Phosphate (C_P)	16 ml. per minute.

Twenty-four-hour creatinine clearances gave results similar to that shown above; the mean of 10 days was 61 ml. per minute. There was no appreciable change as potassium was replenished. Twenty-four-hour potassium clearances (10 to 20 ml. per minute) always remained within the customary normal range.

7. *Renal histology* (Plate 4). At the time of cholecystectomy, almost five months after potassium replenishment, both kidneys were carefully palpated and a small biopsy specimen taken. The kidneys were smooth, and of normal shape and consistency; the histological report by Professor A. C. P. Campbell was as follows: 'The two small fragments of kidney show an active pyelonephritis of subacute or early chronic stage. There is a profuse patchy interstitial infiltration by lymphocytes and plasma cells; in the areas where this is most severe the tubles are dilated and atrophic, and contain colloid casts; most of the glomeruli remain normal, but some show hyalinization. There is little collagenous fibrosis. It is difficult to assess the state of the tubular epithelium in the less affected areas; unfortunately the fixation has been unsatisfactory, and there is a great deal of artefactual disruption of the cells, especially in the proximal convoluted tubles. The amount of this is unexpected in view of the method of fixation, and it may be due to a true underlying abnormality; the less disrupted cells do show some vacuolation. One can draw no definite conclusion on this point.' (Note: the renal biopsy specimen was placed in formol-saline by the authors themselves within one minute of removal from the body.)

8. *The renal excretion of potassium.* The continued excretion of considerable amounts of potassium in the urine of this patient, in spite of the low plasma level and reduced body content of potassium, indicates that her renal disease was at least partly responsible for the state of depletion. In Fig. 2 the behaviour of the patient's kidneys is illustrated by relating the daily excretion of potassium in the urine to the plasma-potassium level; the 29 points charted were obtained during restitution and subsequent maintenance of body-potassium. Potassium salts used for restitution were given in four doses daily, and the blood samples were invariably taken at noon, six hours after the previous dose of potassium salts. For comparison, in the same diagram, are included data showing the functional performance of normal kidneys in the presence of potassium depletion. The normal data were obtained from published accounts of experimental potassium depletion (Black and Milne, 1952; Fourman, 1954; Evans, Hughes Jones, Milne, and Steiner, 1954), and from a single instance of potassium deficiency of alimentary origin (Schwartz and Relman, 1953, Case 1); the charted points cover both the period of depletion and the subsequent period of replenishment. It will be seen from Fig. 2 that the distinctive renal abnormality in the patient was the disproportionately high potassium excretion at low plasma-potassium levels. The potassium clearance of about 14 ml. per minute, and daily potassium excretion of 40 to 50 mEq., when the patient had a plasma level of 2·5 mEq. per litre, are to be compared with a clearance value of 3 ml. per minute and daily output of less than 10 mEq., at a corresponding plasma level, in subjects with normal kidneys. When the patient's plasma-potassium had been restored to normal levels, between 4 and 5 mEq. per litre, the daily excretion of potassium in the urine was no greater than in the normal subjects (Fig. 2), suggesting that dietary privation was necessary to bring out the failure of renal conservation. The patient, however, displayed a general inflexibility in the renal handling of potassium: whereas the normal subjects showed a ten-

fold variation in the potassium clearance between the highest and lowest plasma levels, potassium clearance in the patient varied only from 10 to 20 ml. per minute over the whole range of serum-potassium from 2·5 to 6·3 mEq. per litre. Particular attention might be directed to the three points to the top right of Fig. 2, where the plasma-potassium level exceeded 6 mEq. per litre. These figures were obtained when restitution was complete (Figs. 1 and 5), but

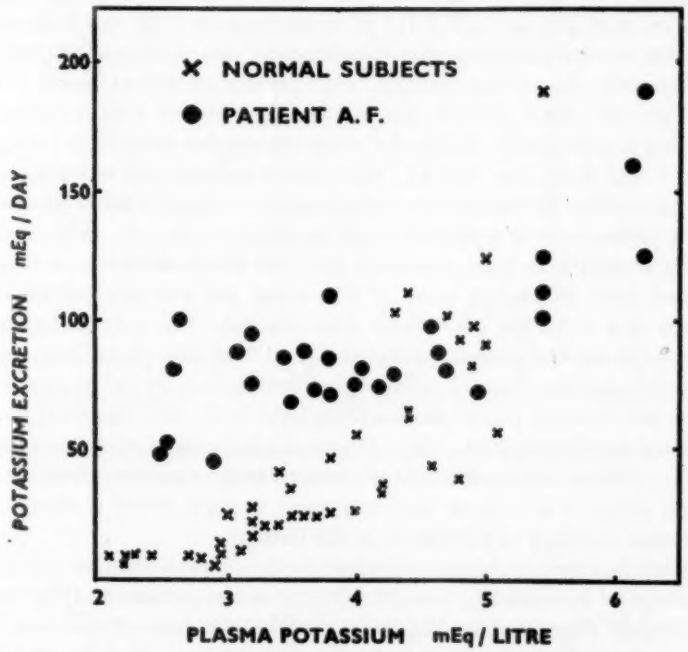

FIG. 2. The relationship between plasma-potassium levels and the urinary output of potassium in normal subjects and in the patient.

before the dose of supplementary potassium salts was reduced. It would seem that, when body-stores of potassium were replenished, the kidneys could not dispose of the moderately high potassium intake (about 200 mEq. daily; see Fig. 1) without elevation of the plasma-potassium to potentially dangerous levels. A person with normal kidneys can dispose of such a dietary intake without much change of plasma-potassium level (see, for example, Evans and Milne, 1954). It is, however, difficult to relate the development of hyperkalaemia in our patient with certainty to her primary renal disease, since a similar occurrence has been recorded during correction of potassium deficiency resulting from alimentary losses (Schwartz and Relman, 1953, Case 2). This particular abnormality may, therefore, be related to the secondary effects of potassium deficiency on the kidneys (see below); we have not had the opportunity to investigate the question whether our patient regained a normal capacity to excrete potassium loads.

9. *The urinary excretion of phosphorus and the changes in plasma-phosphorus.* When observations were begun, the plasma level of inorganic phosphorus was very low (1·24 mg. per 100 ml.), and the daily excretion of phosphorus in the urine was within normal limits (500 to 600 mg. with a dietary intake of 1·2 mg.; see Fig. 1). The renal clearance of phosphate, calculated from the 24-hour phosphate excretion and the plasma-phosphate level at midday, was approximately 20 ml. per minute. This corresponds to a phosphate/inulin clearance ratio (C_P/C_{in} or C_P/G.F.R.) of approximately 0·33, and indicates that the tubules were reabsorbing only two-thirds of the phosphate filtered at the renal glomeruli. In normal subjects, with plasma-phosphate levels of 2 to 4 mg. per 100 ml., the C_P/G.F.R. lies in the range 0·01 to 0·12 (Lambert, Van Kessel, and Leplat, 1947). Normally, when the plasma-phosphate level falls to between 1 and 2 mg. per 100 ml., the tubules reabsorb all but traces of the filtered phosphate. There was thus indisputable evidence of renal phosphaturia when the patient was in a state of gross potassium depletion. With treatment the plasma-phosphate level increased and the renal clearance of phosphate diminished until, at plasma levels of 3 to 4 mg. per 100 ml., normal 24-hour clearances of 8 to 14 ml. per minute were reached. Fig. 3(C) shows the relationship between the plasma-phosphate level and the phosphate clearance before and during the phase of potassium replenishment. It will be seen that the clearance fell with the rise in plasma-phosphate level, until the renal phosphaturia effectively disappeared. Since the renal clearance of phosphate *increases* in normal subjects with an increase of plasma-phosphate (Milne, Stanbury, and Thomson, 1952), it is evident that treatment brought about a change in the renal tubular handling of phosphate in the patient.

Attention has previously been directed to the observation that the plasma-phosphate level increased in parallel with the serum-potassium (Fig. 5). This fact is further illustrated in Fig. 4(A), and the closeness of the relationship suggests that replenishment of body-potassium was responsible for the increase of plasma-phosphate and the changed renal handling of phosphate. We believe this to be the correct explanation of the demonstrated change in tubular function; but the situation is complicated somewhat by changes in the acid-base balance of the extracellular fluids. The large dose of ammonium chloride given at the beginning of the study, and the subsequent administration of KCl (Fig. 1), produced a metabolic acidosis that was not corrected until the patient was receiving her supplement of potassium bicarbonate. Thus, while correcting the major part of the potassium deficit, we were simultaneously correcting the induced acidosis and raising the plasma-bicarbonate level (see Fig. 1). In consequence there was also a good correlation between plasma-phosphate and plasma-bicarbonate levels (Fig. 4(B)). Moreover, although there was a close inverse correlation between plasma-potassium and phosphate clearance (Fig. 3(A)), there was an equally good inverse correlation between plasma-bicarbonate and phosphate clearance (Fig. 3(B)). Since it is generally agreed that a metabolic acidosis will increase the phosphate clearance, the data charted in Fig. 3 do not permit distinction between the effects of potassium replenishment

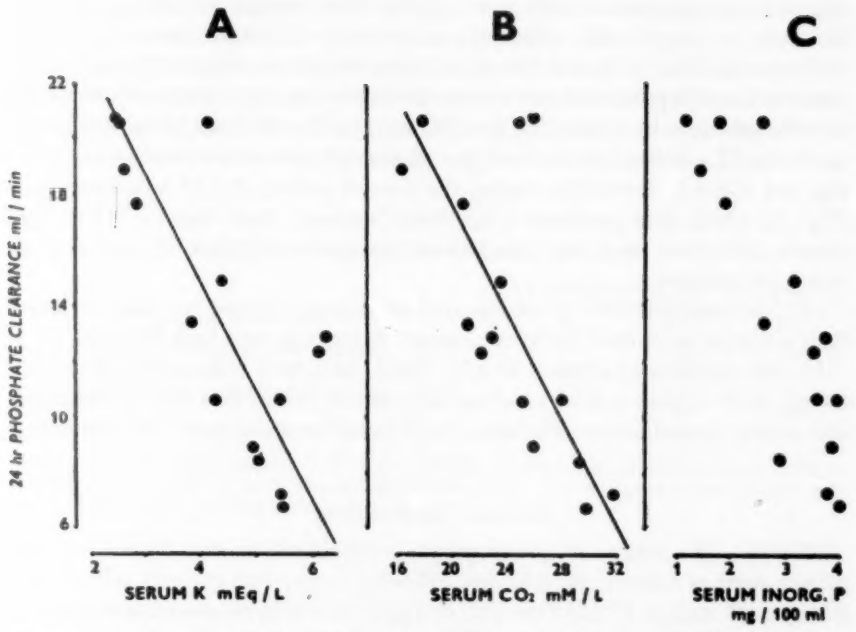

FIG. 3. The relationships between the 24-hour phosphate clearances and the serum levels of (A) potassium, (B) bicarbonate, and (C) inorganic phosphorus.

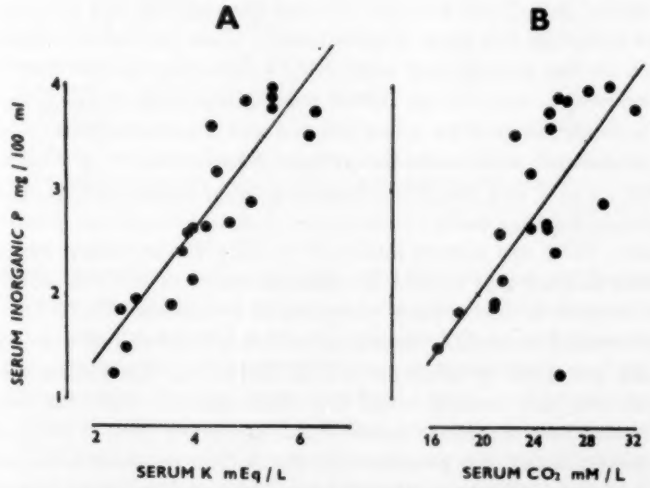

FIG. 4. Relationships between the serum levels of inorganic phosphorus and the serum levels of (A) potassium, (B) bicarbonate.

and those of changes in acid-base balance. Two further considerations may be offered to support the contention that change in potassium economy was the important factor. In the first place, when the patient originally came under observation with potassium deficiency, she was not acidotic (serum-bicarbonate 26 mM. per litre, or 58 ml. CO_2 per 100 ml.), yet the 24-hour phosphate clearance was 22 ml. per minute, and the plasma-phosphate level as low as 1·24 mg. per 100 ml. Secondly, during the second period of KCl administration (Fig. 1), which also produced a metabolic acidosis, there was no fall in the plasma-phosphate level, and the 24-hour phosphate clearance did not exceed 14 ml. per minute.

10. *The renal excretion of calcium and magnesium* showed no changes other than could be accounted for by concurrent changes in acid-base balance.

11. *The excretion of adrenal steroids.* The excretion of 17-ketosteroids (4·0 to 4·7 mg. in 24 hours) and of 17-ketogenic steroids (9·8 to 10·0 mg. in 24 hours) was within normal limits. Facilities for aldosterone assay were not available.

Metabolic Balance Data

Methods. The results of quadruplicate analysis of the diet chosen by the patient were as follows: K, 2·42 gm. (62 mEq.); Na, 1·29 gm. (56 mEq.); Cl, 2·24 gm. (63 mEq.); P, 1·215 gm.; N, 11·2 gm. Any food rejected was collected, and analysed at least in duplicate. Faeces were collected and analysed in two- or three-day periods; urine was analysed daily. Collections were started after the patient had taken the diet for two days. On the third day she received 11 gm. (206 mEq.) NH_4Cl ($\equiv$ 2·88 gm. N), and the chloride was excreted slowly during the following five days. Consequently, when potassium replenishment was started on the seventh day after NH_4Cl (10th day of the diet), she was barely in electrolyte equilibrium. Other recognized defects in the plan of study were our inability to measure water balance and the impossibility of frequent weighing on account of the muscular paresis. Results are shown diagrammatically in Figs. 1 and 5, and numerical data relating to critical phases of the study are included in Tables I to V.

Potassium. With the dietary intake of 62 mEq. K the patient was in potassium balance (Figs. 1 and 5), and the administration of 206 mEq. NH_4Cl produced no increase in the urinary excretion of potassium (Table I). Urinary excretion increased perceptibly as soon as the intake of potassium was augmented to 200 mEq. per diem by addition of KCl (Table II). Equivalence of intake and output was not reached until the 17th day of replenishment, when 1,400 mEq. had been retained. At this time the serum level of potassium was 6·2 mEq. per litre, and it is possible that the patient retained more potassium than she had originally lost. On withdrawal of the potassium supplement (day 28) the external potassium balance became negative (Figs. 1 and 5), and 400 mEq. K were lost in five days (Table III); the serum-potassium level was then 4·95 mEq. per litre. Taking into account the fact that the patient had received 250 mEq. K before our studies began, we conclude that her original

deficit lay between 1,000 and 1,500 mEq. Some effects accompanying the start of replenishment with KCl are shown in Table II. The chloride produced a metabolic acidosis comparable to that previously induced by NH_4Cl, and the initial renal response to each stimulus was similar in that potassium excretion was little changed. On the other hand, when KCl was given, with achievement of a small positive potassium balance, considerable quantities of potassium

TABLE I

Effects of Ammonium Chloride Acidosis

Period of observation	*Daily urinary excretion (mEq.)*		
	K	*Cl*	*Na*
Mean of 2 days before administration of NH_4Cl	47	39	62
On day of administration of 206 mEq. NH_4Cl	47·5	68	69
1st day after administration of 206 mEq. NH_4Cl	47·5	105	88
2nd " " " "	42	82	76
3rd " " " "	46	82	87

Note that, after administration of 11 gm. NH_4Cl, (1) there was no increase in potassium excretion, and (2) the chloride was excreted slowly over a five-day period, and sodium was the principal accompanying cation.

TABLE II

Effects of Potassium Chloride Acidosis

Period of observation	*Daily external potassium balance (mEq.)*	*Daily urinary excretion (mEq.)*		
		K	*Cl*	*Na*
Mean of 2 days before start of potassium replenishment	−2	35	55	47
1st day of supplement, 134 mEq. KCl	+134	44	68	55
2nd day of supplement, 134 mEq. KCl	+115	62	127	56
3rd day of supplement, 100 mEq. $KHCO_3$ and 34 mEq. KCl	+85	103	95	93

Note that the response in terms of potassium excretion, after the first day of KCl treatment, was similar to the response to NH_4Cl administration; there was no significant change in potassium output (see Table I). When a positive cumulative balance of between 200 and 300 mEq. had been achieved, potassium excretion was greatly augmented.

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Sodium and chloride. During the first week there was a negative sodium balance of 205 mEq., exactly equivalent to the excess of chloride given as NH_4Cl at the beginning of the week. It appeared that chloride excretion was largely responsible for this negative balance (Table I). A further increase in sodium output followed KCl administration (Table II), and by the 12th day of study the negative sodium balance was 289 mEq. The serum-sodium level fell

TABLE III

Chloride, Sodium, and Potassium Balance Data

Day	*Comment*	*Weight (kg.)*	*Serum Cl (mEq./l.)*	*ΔCl (mEq.)*	*Serum Na (mEq./l.)*	*ΔNa (mEq.)*	*Serum K (mEq./l.)*	*ΔK (mEq.)*
6	5th day after NH_4Cl. .	57·3	108·5	+76	135	−183	2·86	−21
10	After 2 days KCl . .	..	108	+340	126	−248	2·64	+350
22	After 13 days $KHCO_3$.	61·3	101	+456	138	+11	5·45	+1328
28	After 6 days KCl . .	..	107	+924	131	−98	6·27	+1436
33	5th day after withdrawal of KCl	62·7	104	+700	136	−32	4·95	+1043

'Day' refers to the day of balance study, as in Figs. 1 and 5.
Δ (Cl, Na, K) refers to the cumulative changes in external balance from the start of the study (day 1).

from 136 mEq. to 126 mEq. per litre (Fig. 1). On administration of $KHCO_3$ the position was effectively reversed; the urinary excretion of sodium diminished, the daily sodium balance became positive, and the serum-sodium level increased progressively (Fig. 1). During the 13 days of treatment with $KHCO_3$, 300 mEq. of sodium were retained, and this gain made good the deficit induced by the previous administration of chloride salts. The serum-sodium level was restored to 138 mEq. per litre (Fig. 1). From the balance data it appeared that at the end of this period (day 22, Table III; Fig. 1) the total body-sodium was no greater than at the beginning of the study (day 1). In contrast, the clinical state, with gain of weight and the disappearance of thirst and desiccation, reflected an expansion of the extracellular fluid volume. It is obvious that any such expansion must have resulted solely from extrusion of sodium from cells as potassium was restored. Assuming that chloride does not penetrate body-cells, and that the extracellular fluid volume on day 22 was equivalent to 20 per cent. of the body-weight (12·3 litres), the changes in extracellular fluid volume and in its electrolyte content can be calculated from the changes in plasma-electrolyte levels and external balances (Table III). On this basis, between day 6 and day 22 (see Table III) the extracellular sodium increased by 630 mEq., of which only 194 mEq. was accountable by positive external balance. Thus, as some 1,300 mEq. of potassium were taken up by body-cells, 436 mEq. of sodium were extruded from cells into the extracellular fluid. Although we are not convinced of the validity of the basic assumptions, the calculated 4·4 litres of increase in extracellular fluid volume approximated to the 4 kg. increase in weight.

Chloride was retained, with resultant hyperchloraemia, whenever it was administered in significant dosage as either the ammonium or the potassium salt (Fig. 1; Tables I, II, III). The retained chloride was excreted slowly

during several days after withdrawal of the chloride supplement. A positive chloride balance, to the extent of about 35 mEq. per diem, also developed during treatment with $KHCO_3$, and on the sixth day of its administration chloride was virtually absent from the urine (see Fig. 1). These changes occurred in parallel with the retention of sodium (see Fig. 1) to which reference has already

TABLE IV

Nitrogen Balance Data

Period (days)		*Intake (gm.)*	*Output (gm.)*	*Balance (gm.)*	*Average daily balance (gm.)*
1	(NH_4Cl (≡ 2·88 gm. N)) . .	14·1	12·0	+2·1	+2·1
2–5	(No K supplement) . . .	40·2	45·1	−4·9	−1·2
6–7	(No K supplement) . . .	22·5	19·0	+3·5	+1·7
8–10	(KCl supplement) . . .	33·5	21·1	+12·4	+4·1
11–12	($KHCO_3$ supplement) (Temperature 101°–103° F.) . . .	17·2	18·6	−1·4	−0·7
13–22	($KHCO_3$ supplement) . . .	108	70	+38	+3·8
23–28	(KCl supplement . . .	67·4	48·6	+18·8	+3·1
29–36	(No K supplement) . . .	90	73	+17	+2·1

The additional nitrogen given as ammonium chloride was not utilized, an equivalent amount of nitrogen being recovered in the urine during the subsequent two days.

TABLE V

Phosphorus Balance Data

Period (days)		*Intake (gm.)*	*Output*			*Balance (gm.)*
			Faeces (gm.)	*Urine (gm.)*	*Total (gm.)*	
1–7	('Control') . . .	7·76	3·52	3·81	7·33	+0·43
		(1·11)	(0·50)	(0·54)	(1·05)	(+0·06)
8–9	(KCl supplement)*	2·43	0·57	0·98	1·55	+0·88
		(1·21)	(0·28)	(0·49)	(0·77)	(+0·44)
10–15	(1st phase $KHCO_3$) .	6·59	1·22	1·83	3·05	+3·54
		(1·10)	(0·20)	(0·30)	(0·51)	(+0·59)
16–22	(2nd phase $KHCO_3$) .	8·50	4·38	2·81	7·19	+1·31
		(1·21)	(0·63)	(0·40)	(1·03)	(+0·19)
23–28	(KCl supplement) .	7·29	3·13	3·44	6·57	+0·72
		(1·21)	(0·52)	(0·57)	(1.09)	(+0·12)
29–36	(No K supplement) .	9·72	4·60	4·91	9·51	+0·21
		(1·21)	(0·57)	(0·61)	(1·19)	(+0·03)

Figures in parentheses represent daily averages for the period.

* It is realized that a two-day collection period is of very doubtful significance in indicating a change of phosphorus balance. The patient was, however, passing soft stools daily, and the data are thus charted because they suggest that phosphorus retention increased as soon as potassium replenishment began with the administration of KCl.

been made; 332 mEq. of chloride were retained in company with 300 mEq. of sodium. As will be seen from Table III, the final six days of KCl administration (≡ 804 mEq. Cl) produced a further chloride retention of 468 mEq., and this was associated with a negative sodium balance of 109 mEq. This additional chloride may have been accommodated in a greatly expanded extracellular fluid, in which event large amounts of sodium must have entered the extracellular

fluid from cells or bone. A more likely occurrence is that a part of the retained chloride left the extracellular fluid compartment, possibly to enter erythrocytes (Swan and Pitts, 1955).

Nitrogen and phosphorus. Nitrogen balance data are detailed in Table IV. No more than 0·7 gm. of nitrogen was retained during the preliminary week of observation. Subsequently, as potassium was being rapidly accumulated, the

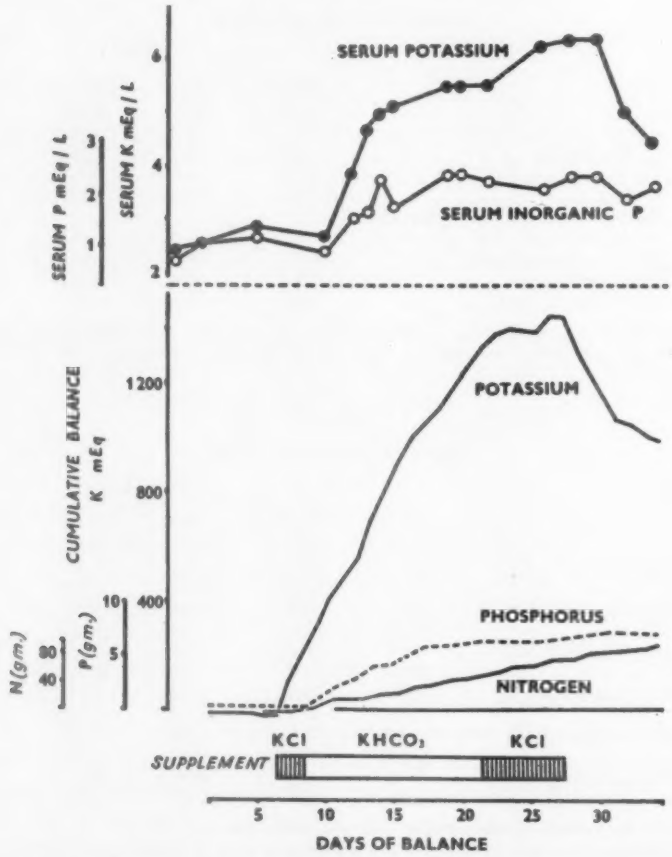

FIG. 5. The cumulative balances of potassium, phosphorus, and nitrogen; the relationships between serum levels of potassium and phosphate and the corresponding external balances.

nitrogen balance became strongly positive, and about 4 gm. N were retained daily. Nitrogen retention continued, except during the short febrile episode (Table IV), throughout the whole period of study, and the patient was still gaining about 2 gm. N a day when metabolic observations were discontinued. The total observed nitrogen accumulation (90 gm.) was equivalent to the formation of approximately 0·5 kg. of body-protein. Further balance studies, made

during two subsequent periods in hospital when the body-potassium was restored, showed that the patient was then in nitrogen equilibrium when taking in her diet 11 gm. and 13 gm. N respectively. The patient was in positive phosphorus balance during the control period, but with the administration of potassium there was a greatly increased phosphorus retention (Table V), reflected in the rapidly rising serum-phosphate level (Fig. 5). The increased retention appeared to result from a decrease in the output of phosphorus in both urine and faeces. We have already suggested that restoration of body-potassium resulted in increased reabsorption of phosphate by the renal tubules; the data of Table V suggest that potassium replenishment may also have increased phosphorus absorption from the gut. It may be noted that the greater retention of phosphorus ($\equiv$ 0·55 gm. per diem) took place during the early days of potassium restitution (days 8 to 15, Table V); thereafter the output, especially in the faeces, increased, the daily retention became progressively smaller (0·19 to 0·12 gm.), and there was no further significant rise in the serum-phosphate levels. During the 36 days of balance study the patient retained a total of 7·1 gm. phosphorus. In Fig. 5 are shown the cumulative balance data for nitrogen, phosphorus, and potassium; the scales on the ordinate are chosen to present these substances in the relative proportions found in normal cell-matter or protoplasm (Reifenstein, Albright, and Wells, 1945). It is evident that potassium was retained greatly in excess of nitrogen, and it can thus be assumed that the original loss of potassium was greater than could be accounted for in terms of tissue breakdown from starvation or infection. The same appears to be true of phosphorus, although the loss of this element was proportionately much less than that of potassium. Of the phosphorus that was retained in excess of nitrogen, approximately 0·12 gm. can be accounted for by the increase of serum inorganic phosphorus and expansion of the extracellular fluid. The remainder, which amounted to about 0·9 gm. by the end of the study, may have entered cells to form ester phosphorus, or may have been deposited with calcium in bone.

Observations on Carbohydrate Metabolism

The results of glucose-tolerance tests are shown in Table VI. When the patient was grossly depleted of potassium, and also after most of the deficit had been made good, there was a sustained moderate hyperglycaemia; later curves were within normal limits. In a patient with chronic cholecystitis and liver damage one cannot safely ascribe this mild diabetes to potassium depletion; but a similar abnormality has been observed in other potassium-deficient patients (Eliel, Pearson, and Rawson, 1950), and in rats with prolonged potassium depletion (Gardner, Talbot, Cook, Berman, and Uribe, 1950). The data shown in Table VII were obtained during the first glucose-tolerance test of Table VI. After ingestion of glucose in the potassium-depleted state, the blood-lactate increased and the serum-potassium and serum-phosphate levels fell, as in normal individuals. Thus, even though associated with mild biochemical

diabetes, the gross deficiency of cellular potassium appeared not to prevent normal peripheral utilization of glucose.

Observations on Muscle Function

It was not possible to carry out electromyography at the height of the patient's muscular paralysis. Subsequent examination (April 7) by Dr. M. Birkbeck, at a time when weak voluntary activity had returned, showed no electromyographic abnormality in the muscles tested. A strength-duration curve of neuromuscular excitability was within normal limits (Ritchie, 1944), and indistinguishable from the curve obtained a year after potassium restitution. In the absence of any clear indication of depressed muscle excitability, we sought evidence of disordered muscle metabolism as an alternative cause for the continued muscular weakness. As a crude approach to this problem we observed the formation of lactic acid by the forearm muscles during ischaemic exercise, using the technique of McArdle (1951). The test was done before beginning potassium

TABLE VI

Glucose-tolerance Tests

For 14 days before the first test the patient received a diet of 2,000 calories, containing 230 gm. carbohydrate, 70 gm. protein, and 90 gm. fat. The same diet was continued during the 14 days of potassium supplements before the second test. The other two tests were done when the patient was taking a free diet of unknown composition.

		Blood-sugar (mg./100 ml.) (minutes after 50 gm. oral glucose)					
Date	*State of body-potassium*	*0*	*30*	*60*	*90*	*120*	*180*
April 13, 1954	Gross depletion. Serum-K 2·9 mEq./l.	77	133	177	197	201	167
April 26, 1954	+1,100 mEq. Serum-K 5·5 mEq./l.	73	152	181	211	201	162
August 13, 1954	Presumed normal. Before cholecystectomy. Serum-K 3·8 mEq./l.	77	137	167	157	128	109
December 17, 1954	Presumed normal. Four months after cholecystectomy. Serum-K 5·0 mEq./l.	118	172	182	177	152	118

TABLE VII

Changes in Blood-Lactate and in Serum Levels of Potassium and Inorganic Phosphorus after the Ingestion of Glucose

	Minutes after 50 gm. oral glucose		
	0	*30*	*135*
Blood lactic acid (mg./100 gm.)	5·6	9·8	20·6
Serum inorganic phosphorus (mg./100 ml.)	2·5	2·7	1·35
Serum-potassium (mEq./l.)	3·2	3·1	2·4

replenishment, and it was repeated after induction of a metabolic acidosis with ammonium chloride. The results are shown in Table VIII, together with comparable observations in normal subjects. Lactate formation with a less severe form of exercise appeared no less efficient than in the normal subjects. Without information on the rate of muscle blood-flow, no strict comparison between the normal and potassium-deficient is possible; but it seems reasonable to conclude that there was no significant disturbance of anaerobic glycolysis in the potassium-deficient muscles, either with or without extracellular acidosis. This

TABLE VIII

Lactate formation during Ischaemic Exercise of Forearm Muscles

	Lactate-content of efferent blood from muscle (mg./100 gm.) Minutes after start of ischaemic exercise					
Subject	*Control*	*2·5*	*7·5*	*10*	*15*	*30*	*45–60*
Patient A. F. (serum-CO_2 26 mM./l.) . .	12·1	32·6	25·7	..	22·2	..	13·1
Patient A. F. (serum-CO_2 18 mM./l.) . .	9·2	28·2	..	26·3	..	..	6·3
Normal A . . .	12·3	32·7	31	..	29·2	..	..
Normal B . . .	7·9	40·4	..	..	24	9·8	..

Technique of McArdle (1951): one minute ischaemic exercise; cuff released at two minutes. Normal subjects squeezed a bulb attached to a mercury manometer; A. F. could not elevate the mercury, and she was provided with a water manometer. In all observations the pyruvate-content of the efferent blood increased in proportion to the increase in lactate.

does not, of course, preclude the possibility of a metabolic failure of adenosine-triphosphate formation; for it is during the aerobic phase of muscle metabolism, as pyruvic acid is degraded to carbon dioxide and water, that the greater fraction of the phosphate-bond energy is generated (Lehninger, 1955). It can be shown that potassium leaks out of the muscle during the ischaemic phase of this test, and is taken up again in the first few minutes after release of the circulation (McArdle, 1951; Mahler and Stanbury, to be published). In familial periodic paralysis McArdle (1954) has found that the 'rebound' uptake of potassium is excessive and unduly prolonged. The pattern of potassium movement during the tests on our patient was quite indistinguishable from that found in normal subjects, and the data will not be recorded. The biopsy specimen of rectus abdominis muscle obtained at operation was histologically normal.

Electrocardiographic observations. Electrocardiography, shortly after the patient's original admission to hospital, showed the characteristic changes of hypokalaemia, with prolonged Q–T interval, depressed ST segments, and diphasic T waves of low amplitude (Dr. E. G. Wade). In the course of subsequent metabolic study a further 20 records were obtained, and from these it appeared that the electrocardiogram was not precisely or predictably related either to serum-potassium levels or to total body-potassium. This is in agreement with the conclusions of Schwartz, Levine, and Relman (1954) from their study of a group of patients. The details of our observations will not be recorded.

Discussion

The nature of the renal disorder

1. *The primary renal lesion.* The nature of the primary renal disease is in little doubt; the episodic dysuria, the frank urinary infection, and the renal histology were characteristic of chronic pyelonephritis. It also appears, from the patient's inability to produce a maximally acid urine and to increase ammonia excretion in the presence of metabolic acidosis, that the principal renal functional abnormality was 'tubular acidosis' (Albright, Burnett, Parson, Reifenstein, and Roos, 1946) or 'renal anacidogenesis' (Lundbaek, 1951). This renal tubular disturbance was not an effect of potassium deficiency. Clarke, Evans, MacIntyre, and Milne (1955) have shown that normal persons depleted of potassium develop a reduced capacity for urine acidification; but in our patient the disability persisted long after potassium replenishment, and her potassium deficiency must be regarded as a consequence, rather than as a cause, of her renal tubular abnormality. Reduced capacity for urine acidification, which is essentially an inability to establish the normal maximal hydrion gradient between blood and urine, reflects inadequacy of the tubular mechanisms of hydrion secretion. This might result from a relative unavailability of hydrion in the tubule cells, such as would develop if carbonic anhydrase were destroyed by disease; or it could result from disorganization of the energy-consuming processes secreting hydrion against a concentration gradient. Since the administration of a carbonic-anhydrase inhibitor to our patient resulted in increased bicarbonate excretion, it may be concluded that her renal tissue contained active carbonic anhydrase. This suggests that the tubular disturbance involved the mechanisms actively transferring hydrion from tubular cells to glomerular filtrate; and the low rate of ammonia excretion would follow as a passive result of the higher urinary pH (Pitts, 1948; Stanbury and Thomson, 1952). It seems to the authors that impairment of the function of hydrion secretion, with consequent inability to produce maximally acid urine, is among the commonest acquired tubular lesions in renal disease. One of us (S. W. S.) has seen this functional lesion in other proved cases of chronic pyelonephritis, in renal amyloidosis, in diabetic glomerulosclerosis, in hypertensive disease, in the renal disorder of hyperparathyroidism, and as a complication of the nephrotic syndrome together with glycosuria, aminoaciduria, and potassium depletion. If such loss of the tubular mechanisms of base-conservation always indicates a liability to renal loss of potassium, as is suggested by the metabolic investigations of Albright and his collaborators (1946), it will be obvious that patients with chronic renal disease of many different types may readily develop potassium depletion. We are satisfied that our patient does not fall into the category of 'primary aldosteronism' as recently defined by Conn (1955*a*). In this syndrome renal wastage of potassium results from an excessive renal tubular secretion of potassium under the influence of aldosterone, which is produced in excess by a secreting tumour of the adrenal cortex. The endocrinological investigations possible in our patient are not alone sufficient to exclude this

diagnosis, but the careful manual exploration made at laparotomy by our surgical colleague would be unlikely to leave undetected an adrenal tumour of appreciable size. Other reasons for excluding the diagnosis of primary aldosteronism are discussed elsewhere (Stanbury and Mahler, 1956).

2. *The renal handling of potassium.* In the syndrome of renal tubular acidosis, with impairment of the tubular capacity to secrete hydrion and ammonium, it might be expected that additional potassium ion would be secreted in exchange for sodium reabsorbed from the glomerular filtrate (Berliner, Kennedy, and Orloff, 1951; Berliner, 1952, 1954), and the development of potassium depletion in these patients would be adequately explained. The early investigations of Albright, Burnett, Parson, Reifenstein, and Roos (1946) showed that administration of an acid-ash diet (130 mEq. NH_4Cl daily) to a patient with tubular acidosis produced little increase in ammonium excretion; instead, the output of potassium was considerably increased, leading to a negative potassium balance and symptoms of potassium deficiency. We have little doubt that similar mechanisms were involved in the production of potassium depletion in our patient; but there are aspects of her renal handling of potassium that elude satisfactory explanation. When a normal subject becomes deficient of potassium the healthy kidney conserves it, and stimuli that would normally increase the urinary output of potassium become relatively ineffective (Evans, Hughes Jones, Milne, and Steiner, 1954); large doses of ammonium chloride produce only small increases in potassium excretion (Clarke, Evans, MacIntyre, and Milne, 1955). Administration of ammonium chloride to our patient, when she was potassium-depleted, produced no increase in the urinary output of potassium. In respect of this particular stimulus the diseased kidneys were apparently able to conserve potassium, as the normal kidney does in potassium deficiency; on the other hand, once potassium had been replenished, ammonium chloride produced the expected increase in potassium excretion. One is thus faced with the paradox that kidneys, already leaking 40 to 50 mEq. of potassium daily despite gross body depletion, were apparently capable of resisting a stimulus to further potassium loss. It may be suggested that the continued wastage of potassium in the urine was due to defective reabsorption of filtered potassium; and if this was the case the initial response to ammonium chloride may indicate that the secreting mechanisms were conserving potassium normally in the presence of potassium depletion. If, alternatively, potassium wastage was due to continued morbid activity of the potassium-secreting mechanisms of the renal tubule, the stimulus responsible for this activity is not apparent. One must again emphasize the fact that the rate of potassium clearance was never greater than one-third of the simultaneously measured glomerular filtration rate. In primary aldosteronism, where the potassium-secreting mechanisms are stimulated to excessive activity (Conn, 1955*a*), potassium clearance may approach the filtration rate (Evans and Milne, 1954) or even exceed it (Earle, Sherry, Eichna, and Conan, 1951). In renal excretory failure potassium clearance commonly exceeds the rate of glomerular filtration (Platt, 1950). If we invoke continued tubular secretion as an explanation of the continued

potassium wastage in A. F. when she was deficient of potassium, we must envisage a restricted or submaximal activity incapable of augmentation by stimulation with ammonium chloride. Moreover, it was not augmented sufficiently to protect the patient from potential potassium intoxication once the body-potassium had been replenished. In the present state of our knowledge we can offer no satisfactory explanation for these phenomena.

3. *Secondary effects of potassium depletion on the kidney.* There is evidence that, in subjects with previously normal kidneys, depletion of potassium may give rise to a variety of renal functional disturbances, and even to characteristic histological changes in the renal tubules (Schwartz and Relman, 1953; Clarke, Evans, MacIntyre, and Milne, 1955; Stanbury and Mahler, 1956). It will be obvious that, if potassium depletion results from renal disease, the patient may develop additional renal changes in consequence. In the present patient we consider potassium deficiency to have been responsible for renal phosphaturia, and for failure of the renal conservation of sodium chloride; it may also account for a reduced osmolar concentrating capacity, and for some of the histological findings in the renal biopsy.

The evidence relating potassium depletion and renal phosphaturia in this patient has been discussed in detail, together with the complicating influence of changes in acid-base balance. In another patient, a nephrotic child with acquired tubular acidosis and potassium depletion, administration of potassium bicarbonate produced a similar fall in phosphate clearance without correcting extracellular acidosis (Macaulay and Stanbury, unpublished observations). Primary losses or gains of body-potassium are usually associated with a smaller concomitant loss or gain of body-phosphorus; and there is evidence that the kidney is at least partly responsible for the secondary effects on phosphorus metabolism (Stanbury and Mahler, 1956). The observed renal phosphaturia in the patient A. F. may, therefore, be better considered as a physiological than as a pathological consequence of potassium deficiency. It would be of interest to know whether a patient such as ours, having phosphaturia in association with potassium depletion, would continue to lose phosphorus in the urine if given a diet of low phosphorus-content, or whether the renal loss of phosphorus would remain proportionate to loss of potassium. In the latter case one might regard the phosphorus excretion as a manifestation of the well-known biological relationship between phosphorus and potassium; the former alternative would suggest some morbid disturbance of the phosphate-reabsorbing mechanisms of the renal tubule. There is no way of distinguishing between these alternatives in our patient, but the continued phosphate excretion, despite exceptionally low plasma-phosphate levels, seems to us to indicate a pathological tubular disorder.

When the patient had gross potassium depletion, she was excreting daily in her urine approximately the same amount of sodium and chloride as she was receiving in her diet. A renal response more appropriate to her state of clinical desiccation would have been the excretion of urine with negligible sodium-chloride content, until such time as her extracellular-fluid deficit had been made good. It became apparent that the kidneys were actually capable of such

a response for on treatment with potassium bicarbonate the urinary output of sodium and chloride fell progressively. On the sixth day of $KHCO_3$ administration (day 15, Fig. 1) the urinary concentration of sodium was 6 mEq. per litre, and of chloride <1 mEq. per litre; and the urinary volume had fallen to about a litre, compared with the 1·5 to 2 litres daily before this treatment. It was unfortunate that $KHCO_3$ administration coincided with the onset of an acute

TABLE IX

Potassium Balance and Urinary Output of Sodium

Period	Potassium			Sodium		
	Intake (*mEq.*)	*Urinary output* (*mEq.*)	'*Balance*' (*mEq.*)	*Intake* (*mEq.*)	*Urinary output* (*mEq.*)	'*Balance*' (*mEq.*)
Five days without K supplement	290 (58)	401 (80)	−111 (−22)	285 (57)	376 (75)	−91 (−18)
Two days with supplementary $KHCO_3$ (150 mEq./day)	416 (208)	166 (83)	+250 (+125)	114 (57)	109 (54)	+5 (+2)

July 1954. Observations were terminated when the patient had to leave hospital for domestic reasons.
Faeces were not collected. Figures in parentheses represent daily averages for the period.

TABLE X

Potassium Balance and Urinary Output of Sodium and Chloride

Period	Potassium			Sodium			Chloride		
	Intake (*mEq.*)	*Urinary output* (*mEq.*)	'*Balance*' (*mEq.*)	*Intake* (*mEq.*)	*Urinary output* (*mEq.*)	'*Balance*' (*mEq.*)	*Intake* (*mEq.*)	*Urinary output* (*mEq.*)	'*Balance*' (*mEq.*)
Six days without K supplement	372 (62)	446 (74)	−74 (−12)	336 (56)	528 (88)	−192 (−32)	378 (63)	446 (74)	−68 (−11)
Six days with $KHCO_3$ (40 mEq. for 4 days; 60 mEq. for 2 days)	652 (109)	403 (67)	+249 (+41)	336 (56)	370 (62)	−34 (−6)	378 (63)	421 (70)	−43 (−7)

August 1954. Faeces were not collected. Figures in parentheses refer to daily averages for the period.
Cholecystectomy was done two days after the end of the second period.

febrile urinary infection, as it may reasonably be argued that this episode, rather than potassium restitution, was responsible for the retention of sodium chloride. Further data relevant to this problem are shown in Tables IX and X, which relate to additional metabolic studies performed on two subsequent admissions of the patient to hospital. It will be seen that, unless she was receiving more than 70 to 80 mEq. of potassium daily, she was in negative potassium balance; and in this state she also lost 20 to 30 mEq. of sodium daily. Production of a positive potassium balance by $KHCO_3$ supplements corrected the tendency to renal wastage of sodium. Potassium bicarbonate thus produced similar effects in each of three metabolic studies; and it is reasonable to conclude that the state of body-potassium in some way determined the efficiency of sodium conservation by the kidney. It would be unwise to speculate on the nature of this effect, but one may note that it was exerted more obviously on

sodium than on chloride (Table X), suggesting an action on cation-exchange mechanisms in the renal tubule. If replenishment of potassium increased the tubular secretion of this ion, one might expect an increased reabsorption of sodium in exchange for the secreted potassium. Administration of potassium bicarbonate was always followed by an increase of plasma-bicarbonate, with a

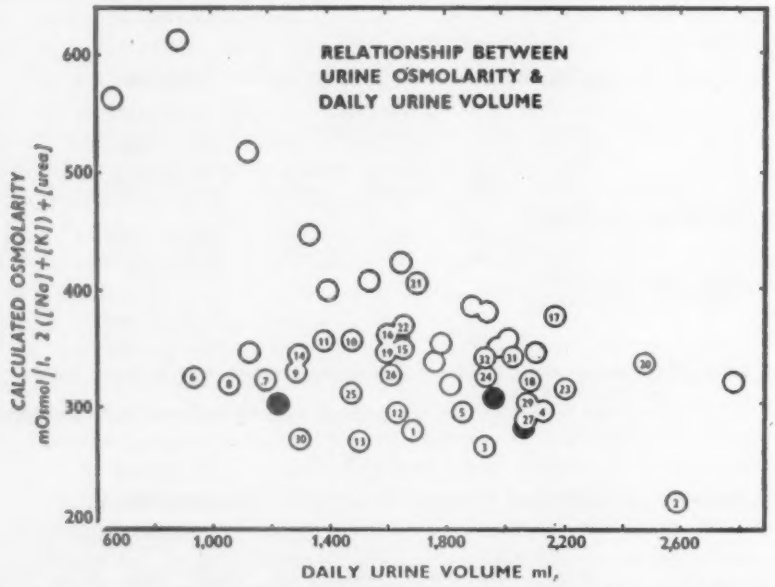

FIG. 6. The apparent effects of potassium replenishment on the osmolar concentrating capacity of the kidneys.

The calculated osmolarity of the 24-hour specimen is related to the daily urine volume. Black circles represent specimens collected before potassium repletion; circles with enclosed numerals represent successive days of potassium therapy. White circles represent specimens obtained four months after potassium repletion.

reciprocal fall in the serum-chloride level (see, for example, Fig. 1), and presumably the latter effect reduced the amount of chloride filtered by the renal glomeruli. It may be this change, rather than an effect on the tubules, that led to a reduction in chloride output.

Schwartz and Relman (1953) described two patients, potassium-depleted from alimentary losses but not suffering from primary renal disease, who were unable to produce a concentrated urine; concentrating capacity was regained after replenishment with potassium. We were not able deliberately to deprive our patient of fluid in her potassium-depleted state, but we have calculated the osmolarity of all 24-hour urine specimens obtained before and during potassium replenishment, and on a subsequent admission some months after potassium depletion was corrected. The results are shown in Fig. 6. During the patient's first stay in hospital the urine osmolarity was never much higher than an average normal value for plasma (310 mOsmol. per litre; Gamble, 1947),

even when the daily urine volume was less than 1,400 ml. Four months after potassium restitution, urine osmolarities almost twice this value were obtained at corresponding rates of urine flow. This result suggests an improvement in concentrating capacity with repair of the potassium deficit.

The structural changes developing in the renal tubules in potassium deficiency are discussed elsewhere, with a description of patients showing such lesions (Stanbury and Mahler, 1956). It seems likely that the 'clear-cell nephrosis' or 'vacuolar nephropathy' of potassium deficiency was responsible for some of the appearances described in the renal biopsy specimen obtained from our patient. Electrolyte analysis of the muscle biopsy specimen suggested that the patient still had a potassium deficiency at the time of operation; this point is discussed further below.

Metabolic effects of potassium depletion

1. *Protein metabolism.* It has long been known, from observations on the urinary output of potassium and nitrogen in starvation, that there is an obligatory relationship between potassium and protein metabolism (Benedict, 1915; Fenn, 1940), and in animals an adequate intake of potassium is essential for growth (Kornberg and Endicott, 1945–6; Smith, Black-Schaffer, and Lasater, 1950; Ruegamer, Elvehjem, and Hart, 1946). In protein-depleted rats an optimal intake of protein is ineffective in producing tissue regeneration unless minimal amounts of potassium are included in the diet (Cannon, Frazier, and Hughes, 1952). The indispensability of potassium for protein synthesis in man is less easily demonstrated, although surgeons have recognized the need for provision of potassium during recovery from a period of starvation (Moore and Ball, 1952). In the patient A. F. the critical role of potassium in protein restitution was clearly defined. There can be little doubt, from her dietary history and from the subsequent prolonged period of nitrogen retention, that she was deficient in protein; yet during the first week of study she was effectively in nitrogen equilibrium with a daily protein intake of 70 gm. In contrast, a highly significant retention of nitrogen became apparent on the first day of potassium replenishment (Table IV). Frost and Smith (1953) have made comparable observations on surgical patients maintained exclusively on intravenous dextrose and protein hydrolysate. Although receiving an adequate caloric and nitrogen intake, the nitrogen balance in some of their patients did not become positive until the first day of potassium therapy. These observations have obvious relevance to any situation in which protein depletion results from starvation or from accelerated protein breakdown. If in addition to protein wastage there is continued loss of potassium through the bowel or kidney, as may be the case in steatorrhoea or with failure of renal conservation, it is unlikely that consumption of an ordinary, or even a high-protein, diet will suffice for complete recovery. The patient with chronic renal disease often develops desiccation from loss of extracellular electrolyte, and the consequent catabolic response produces increased destruction of body-protein. If, as we have suggested earlier, such patients are often deficient in potassium, fluid-replenishment may not be

followed by protein synthesis, and irreparable loss of tissue may result. This combination of catabolic episodes with inefficient protein anabolism may possibly be a factor in the wasting and weakness of patients with renal failure.

2. *Phosphorus metabolism.* The retention of phosphorus that follows restitution of potassium is in part related to the resynthesis of protein. During starvation phosphorus is lost in proportion to loss of tissue-protein, and it is proportionately retained on resumption of feeding (Howard, Bigham, Eisenberg, Wagner, and Bailey, 1946). There is also, during development of potassium depletion, a loss of phosphorus greater than can be accounted for by loss of nitrogen (Black and Milne, 1952; Fourman, 1954), and little is known of its origin. Evidence of a similar loss was seen in the patient A. F., but we can shed no light on the problem of its origin, which must be attacked directly by tissue analysis. Our observations suggest, however, that potassium deficiency may exert effects on the two main regulators of external phosphorus balance—the kidneys and the bowel. Little attention has been given to the possibility that potassium may influence the absorptive activity of the gut as well as its motor function. The present observations suggest that this possibility may repay further study; but, in the absence of data regarding calcium absorption, we are unwilling to lay much stress on the apparently increased absorption of phosphorus produced by potassium replenishment.

3. *Carbohydrate metabolism.* The simple tests that were carried out on A. F. serve only to establish the fact that a patient with an enormous deficit of intracellular potassium could break down muscle glycogen normally to pyruvic and lactic acid during ischaemic exercise, and that the potassium-deficient peripheral tissues (muscles) were able to utilize glucose after its oral administration as well as in the normal state. A crucial outstanding problem is to ascertain whether glucose utilization in potassium-deficient muscles yields a normal complement of phosphate-bond energy. *In vitro* enzymatic studies indicate an essential role for potassium ion in the formation of creatine phosphate and adenosine triphosphate in muscle (Boyer, Lardy, and Phillips, 1942, 1943; Lardy and Ziegler, 1945; Kachmar and Boyer, 1951), and it is conceivable that clinical potassium depletion could reduce the cellular concentration of potassium below the optimum necessary for phosphorylation reactions (Lardy, 1951). Impairment of adenosine-triphosphate formation would account adequately for most of the muscle symptoms of potassium depletion.

4. *Electrolyte metabolism.* From calculations based on the assumption that chloride is an obligatory extracellular anion, it appears that one mole of sodium was extruded from cells for three moles of potassium taken up into cells during potassium replenishment. We have already suggested that the reduced renal capacity for potassium excretion may have led to the retention of more potassium than was originally lost. It is consequently impossible to ascertain accurately the extent to which the original deficit of cellular potassium was replaced by sodium derived from extracellular fluid. As a crude approximation it may be suggested that no more than one-half of the cellular potassium lost by the patient was replaced by sodium; and, if one follows Cooke, Segar, Cheek,

Coville, and Darrow (1952), the remaining deficit of cellular K^+ may be considered as made up by H^+ entering cells from the extracellular fluid. The resulting fall in intracellular pH (Gardner, MacLachlan, and Berman, 1952) may account for the hyperpnoea exhibited by A. F. in her potassium-depleted state.

None of our metabolic investigations will explain the development of extreme thirst as an apparent symptom of potassium deficiency. When A. F. was suffering severely from thirst, the osmolarity of her extracellular fluid was in the low normal range (serum-sodium 136 to 138 mEq. per litre), so that the symptom is not explained by increased tonicity of the whole body-fluid (Wolf, 1950); thirst was alleviated as the potassium deficit was made good, without a significant change in extracellular-fluid osmolarity. The explanation of this symptom may lie in the osmotic behaviour of potassium-depleted cells, or of the particular cells concerned with the central perception of thirst. Little is known as yet of the state of osmotically active solutes within the potassium-depleted cell.

Clinical implications of the present investigation

In a patient found to be sustaining large renal losses of potassium, it is of first importance to decide whether the abnormality results from primary renal disease or from morbid adrenocortical overactivity. Radical removal of a secreting adrenal tumour in primary aldosteronism (Conn, 1955*b*), and adrenal surgery or pituitary irradiation in Cushing's syndrome (Plotz, Knowlton, and Ragan, 1952), offer the possibility of considerable, or even complete, relief. When potassium wastage results from renal disease, therapy resolves itself into compensation of the defective renal homoeostasis, and it may be necessary to continue potassium supplementation until progression of the primary renal disease produces some change in the renal handling of this ion. In certain patients, such as the one reported by Evans and Milne (1954), potassium wastage has been ascribed to renal disease when the correct diagnosis was primary aldosteronism (Cope and Milne, 1955); in consequence, the chance of effecting radical cure has been lost. The methods available for the assay of plasma and urinary levels of aldosterone are as yet insufficiently critical for clinical use in the detection of excessive aldosterone production (Dr. J. F. Tait, personal communication). Distinction between primary renal and primary adrenal causes of 'potassium-losing renal lesions' is thus largely dependent on clinical and metabolic considerations; this question is discussed in detail elsewhere (Stanbury and Mahler, 1956). In addition to the positive evidence of renal disease in our patient A. F., she exhibited two features that further emphasize the difference of her condition from primary aldosteronism as defined by Conn (1955*a*). First, no difficulty was experienced in making good the potassium deficit, and there was even a risk of potassium overdosage. Second, the rate of urinary potassium excretion was never as great as in reported cases of primary aldosteronism, and the renal clearance rate of potassium did not exceed one-third of the glomerular filtration rate.

The patient A. F. provides an instructive illustration of the diagnostic difficulties that may arise when renal disease interferes with the kidneys'

regulatory functions, while leaving excretory function unimpaired. On the basis of thirst and polyuria, one physician diagnosed diabetes mellitus; the painful, red tongue led a house physician to treat the patient for 'vitamin deficiency'. Moreover, as the significance of the almost complete limb paralysis was not at first appreciated, it will be obvious that the chance of diagnosis at the stage of 'muscle weakness' is extremely remote. Before the development of these symptoms the minimal and variable proteinuria would excite little attention, and, with a normal blood-urea level and normal excretory pyelogram, most clinicians would be inclined to dismiss the possibility of significant renal disease. There is no simple answer to this problem. We would suggest that the finding of even minimal proteinuria, a history of previous renal disease, and especially the presence of nocturia, should direct attention to the possibility that homoeostatic renal insufficiency underlies a complaint of vague weakness and ill health. Electrolyte analysis of the plasma and a urine-concentration test of renal function may permit of earlier diagnosis; otherwise the patient will suffer the inevitable fate of one whose organic symptoms simulate the neurotic. The clinical recognition and appropriate treatment of potassium depletion in patients with renal excretory failure and nitrogen retention present even greater difficulties, and it may be thought that the problem does not warrant serious clinical consideration. On the other hand, patients with normotensive azotaemia may live for many years, and the low-protein diet on which they are customarily maintained may also be of low potassium-content and predispose to potassium depletion. If potassium depletion can produce vague muscular weakness, disturb protein metabolism, produce ill-defined cellular disturbances of phosphorus metabolism, and possibly reduce the capacity of the diseased kidneys to conserve sodium, it seems reasonable to assume that the azotaemic patient would benefit from having a normal cellular content of potassium. There is real need for further metabolic investigation in azotaemic patients, coupled with accurate measurements of total body-potassium. The administration of moderate doses of potassium salts to patients with renal excretory failure is hazardous only if the intake of sodium and water is inadequate and urine flow reduced in consequence (Winkler, Hoff, and Smith, 1941; Keith, King, and Osterberg, 1943). In an adequately hydrated patient we should not hesitate to give 30 to 60 mEq. of an alkaline potassium salt daily in divided doses by mouth if there was evidence of a body-potassium deficit. The improvement in tone of feeling that follows rectification of a chronic potassium deficit would alone justify the procedure, and frequent determination of plasma-potassium levels during the first few days of treatment would permit control of dosage.

The mechanisms responsible for electrocardiographic changes and for voluntary-muscle paralysis in potassium depletion will not be considered further; but we shall discuss the paralytic ileus in more detail, as its development reflected unfavourably on our clinical management of the patient. Ileus in patients after operation is commonly associated with hypokalaemia (Randall, Habif, Lockwood, and Werner, 1949; Eliel, Pearson, and Rawson, 1950), and there is suggestive experimental evidence that the paralysis of smooth muscle

results from depletion of cellular potassium (Streeten and Vaughan Williams, 1952). When ileus developed in A. F. there is no doubt that she was again depleted of potassium, and retrospectively we were able to ascertain the reasons for this. The serum-potassium level was normal (3·8 mEq. per litre; Table XII) on the day of cholecystectomy, but muscle obtained at operation had a potassium-content at the lower extreme of normal (Table XI). It is thus probable that

TABLE XI

Electrolyte Analysis of Muscle

	H_2O (*gm./kg.*)	*Cl* (*mEq./kg.*)	*Na* (*mEq./kg.*)	*K* (*mEq./kg.*)	*Fat* (*gm./kg.*)
Rectus muscle (A. F.)	750	11·6	42·0	81·5	61
Normal muscle:					
mean	776·5	19·1	33·7	94·0	..
standard deviation	6·4	3·9	6·4	5·94	

Electrolyte data are expressed as 'per kilogram of fat-free fresh tissue'.
Normal values are those given by Talso, Spafford, and Blaw (1953).
Note the low levels of muscle chloride and potassium; the latter was below the mean normal by an amount more than twice the standard deviation. Muscle sodium was at the upper end of the normal range. The data from A. F. may be contrasted with those in the patient of Fourman and McCance (1955), whose muscle contained more than the normal amount of Na+K. The authors related the excess of intracellular cation to the development of tetany in their patient; it may be recalled that A. F. at no time suffered tetany.

TABLE XII

Urinary Electrolyte and Nitrogen Output after Cholecystectomy

Day after operation	*−1*	*0*	*1*	*2*	*3*	*4*	*5*	*6*
Na (mEq./day)	63	70	55	59	37	31	38	..
Cl (mEq./day)	67	62	43	65	52	39	36	..
K (mEq./day)	74	68	72	90	85	86	97	..
N (gm./day)	8·65	5·0	8·0	11·7	9·0	10·4	12·1	..
Serum-potassium (mEq./l.)	4·0	3·8	..	3·7	..	..	..	3·2

No food and, despite our instructions to the contrary, no potassium supplement, were taken on the day of operation (day 0). Subsequently the patient received 60 mEq. $KHCO_3$ daily. Virtually no food was taken on days 1, 2, and 3; thereafter she was given small quantities of food that could not be measured.
The fall in Na and Cl output following operation was less than that usually seen after laparotomy. The data are to be compared with those obtained by Black and Jepson (1954) and by Davies, Jepson, and Black (1955) in patients managed after operation in a similar manner in the same surgical ward. It is considered that the maintained excretion of sodium and chloride was a further manifestation of the reduced capacity for salt conservation in this patient.

the patient was not replenished with potassium to the optimum level; and it may have been advisable to increase the serum-potassium level to at least 5 mEq. per litre before undertaking surgery. From inspection of Fig. 5 it may be seen that a difference between 4 and 5 mEq. per litre in the serum-potassium of this patient could represent a difference of 200 mEq. in total body-potassium. The day of operation entailed a negative potassium balance of 70 mEq. (Table XII), and, despite a daily intake of 60 mEq. $KHCO_3$, there was probably a small daily loss during the period of semi-starvation following operation. By the sixth day after operation the serum-potassium level had fallen to 3·2 mEq.

per litre, but, as the patient had resumed a normal diet, this finding did not occasion alarm. During the 12th to 14th days after operation, when the patient was ambulant and apparently well, she received in error 20 mEq. instead of 180 mEq. $KHCO_3$; on the 14th day she developed simultaneously lobar pneumonia and ileus with vomiting. The serum-potassium level was then 2·6 mEq. per litre. It is abundantly evident that inadequate potassium intake was responsible for a gross potassium depletion, and it is probable that this, with the pneumonia, was responsible for the development of ileus. We conclude that if a patient with 'potassium-losing nephritis' is to be submitted to essential surgery it is desirable first to bring the serum-potassium level into the high normal range, and secondly to maintain it there by increasing the maintenance dose of potassium salts after the operation.

Acknowledgements

The authors wish to express gratitude to the patient for her co-operation and cheerful willingness to help in the detailed study undertaken. Our thanks are also due to the late Dr. A. H. Holmes for transferring the patient to us for study, and to Professor R. P. Jepson for a somewhat unconventional cholecystectomy. Professor Robert Platt and numerous other colleagues have contributed much useful advice and criticism. The diagrams were prepared in the Department of Medical Illustration, Manchester Royal Infirmary, and the photomicrograph by Miss E. Gibbon of the Department of Medical Photography, Wythenshawe Hospital.

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Summary

A patient is described who, from a combination of anorexia and failure of the renal conservation of potassium, became depleted of about one-half of her total body-potassium. Her symptoms included muscular paralysis, thirst, dehydration, and nocturia. The principal biochemical abnormalities in the plasma were a low potassium level and conspicuous hypophosphataemia; the blood-urea level was normal and, despite an inability to produce maximally acid urine, there was no metabolic acidosis. The biochemical abnormalities were corrected, and all the symptoms but nocturia were relieved, by administration of potassium bicarbonate and a diet of relatively low sodium-content.

Detailed metabolic and renal studies, before and during potassium replenishment, allowed the separation of renal abnormalities attributable to the primary renal disease from secondary functional disturbances resulting from the potassium deficiency. The primary renal disease was shown by biopsy to be chronic pyelonephritis, which led to a reduced glomerular filtration rate and 'tubular acidosis'. Potassium deficiency appeared to be responsible for reversible renal phosphaturia, impaired capacity for sodium conservation, and possibly reduced osmolar concentrating capacity. The renal mechanisms responsible for potassium wastage are discussed in detail.

An attempt was made to study the effects of potassium deficiency on the metabolism of nitrogen and phosphorus, and observations were made on the carbohydrate metabolism of the weakened muscles. These observations appeared to establish the indispensability of potassium for the synthesis of protein in man, and suggested a relationship between body-potassium and the capacity for phosphate absorption by the renal tubules and possibly by the bowel. No abnormality of excitability, or disturbance of lactic acid formation, could be demonstrated in the weak, potassium-depleted voluntary muscles.

Various clinical implications of the study are discussed. It was possible to relate the occurrence of paralytic ileus after cholecystectomy to the inadvertent re-development of potassium deficiency.

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Renal biopsy specimen (×100) showing characteristic changes of chronic pyelonephritis

Note profuse interstitial infiltration with round cells, tubular dilatation, and colloid casts

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ADDENDUM

Aldosterone assay was performed on January 14th, 1955, by Dr. A. H. Gowenlock at the Courtauld Institute of Biochemistry, The Middlesex Hospital. The 24-hour urinary output of aldosterone was 9·3 μg., and of hydrocortisone 34·1 μg. These values are normal for the method used (Ayres, Simpson, and Tait: *Endocrinology*; in the press). Serum-electrolytes at the time of assay were: Na, 144 mEq. per litre; K, 5·1 mEq. per litre; Cl, 104 mEq. per litre; total CO_2, 19·2 mEq. per litre. The 24-hour urinary output of Na was 179 mEq., and of K 97 mEq.

Renal biopsy specimen (×100) showing characteristic changes of chronic pyelonephritis

Note profuse interstitial infiltration with round cells, tubular dilatation, and colloid casts

616.832.9–005.1

SPONTANEOUS SPINAL SUBARACHNOID HAEMORRHAGE[1]

By R. A. HENSON and P. B. CROFT

(From the Neurological Department of the London Hospital and Maida Vale Hospital for Nervous Diseases)

With Plate 5

The advent of percutaneous angiography and the increasing value of surgery in the treatment of cerebral aneurysms and angiomas have aroused new interest in the subject of spontaneous intracranial subarachnoid haemorrhage. The rarer condition of spontaneous spinal subarachnoid haemorrhage is less widely recognized. The distinction of these two forms of meningeal haemorrhage is not always easy, and it is likely that patients with spinal spontaneous subarachnoid haemorrhage are sometimes thought to be suffering from the much commoner intracranial type of bleeding. A survey of the published reports shows that isolated cases of this form of spinal haemorrhage have been described, usually in reviews of the spinal vascular abnormalities. There are few clear accounts of the symptomatology, and no apparent appreciation of the way in which intracranial bleeding may be simulated. The time appears ripe for the description of a series of cases seen by the same observers. We are therefore presenting a group of seven patients who have been under the care of one of us (R. A. H.) or who have been seen in consultation. In addition there are available for consideration the notes of five patients who have died at the London Hospital, and in whom massive spinal subarachnoid haemorrhage was discovered at necropsy.

Literature

Examples of spontaneous spinal subarachnoid haemorrhage in patients with angiomas of the cord have been published by Balck (1900), Lorenz (1901), Robertson (1938), Wyburn-Mason (1943), Trupp and Sachs (1948), and others. Walton (1953), in his paper on subarachnoid haemorrhage of unusual aetiology, included two cases of spinal subarachnoid haemorrhage. The source of bleeding in one case was a spinal angioma, but in the second it was undetermined. Cobb (1915) mentioned a patient described by Gaupp (1888) who almost certainly had a subarachnoid haemorrhage from a venous malformation of the lower part of the spinal cord. Abbott (1939), Krayenbühl (1947), Roger, Paillas, and Duplay (1949), and Fincher (1951) have drawn attention to the occurrence of subarachnoid haemorrhage in patients with intradural spinal neoplasms. Ford (1952) described a child with spina bifida and a haemangioma of the sacrum from which there was intrathecal haemorrhage. Tarlov and Keener

[1] Received August 29, 1955.

(1953) reported a case of spinal subarachnoid haemorrhage in a three and a half months old baby who had a meningeal sarcoma in the cervical region. Other causes include typhoid fever (Douglas-Wilson, Miller, and Watson, 1933) and aneurysm of a segmental spinal artery in association with coarctation of the aorta (Wyburn-Mason, 1943). Wilson (1954) mentions blood dyscrasias, generalized vascular disease, either arteriosclerotic or syphilitic, and toxi-infective states. Michon (1928) gave a clear account of the spinal clinical features of the syndrome under the title of *Le Coup de poignard rachidien.*

Clinical Features

The clinical features of spinal subarachnoid haemorrhage fall conveniently into three groups: (1) the results of the entry of blood into the spinal subarachnoid space; (2) symptoms and signs of intracranial extension of the haemorrhage; (3) the results of damage to spinal cord and nerve-roots. These several aspects of the syndrome are illustrated in the case histories which follow. The haematorrhachis may arise on a background of pre-existent symptoms of disease of the spinal cord or nerve-roots (for example, Case 5). It may be heralded by an attack of herpes zoster (Case 6). It may punctuate the course of polyarteritis nodosa (Cases 8 and 9) or nephritis with hypertension (Case 3). On the other hand the spinal catastrophe may come unannounced.

1. *The results of haemorrhage into the spinal subarachnoid space.* The patient experiences sudden and often agonizing pain in the back; indeed, he may cry out with the intensity of the pain. This is the *coup de poignard* of Michon. The pain is usually felt first at the site of the bleeding, tending to spread as the blood seeps throughout the subarachnoid space. Bilateral sciatica may supervene as the blood passes into the lumbar sac; if, however, the haemorrhage originates in this region, the first pains may be of a sciatic distribution. In four of our patients the *coup de poignard*, with or without sciatica, was experienced (Cases 1, 2, 6, and 7). Root pain at other levels was encountered only in Case 1. Physical examination of our patients revealed signs of spinal meningeal irritation, often of extreme degree: six patients had head-retraction, and three had opisthotonos, the remainder having milder degrees of spinal rigidity. Spasm of the hamstrings, or at least a strongly positive Kernig's sign, was the rule. The following case histories illustrate the syndrome.

Case 1. A man aged 49 years, admitted June 1, 1954 (L.H. No. 18651/52). Twelve days previously he had had a fall from his horse while riding, landing on his left shoulder. Although complaining of pain around the left chest, he continued to ride for the next two days. A week after the injury he was awakened by severe lumbar pain, which radiated down both legs. This intense pain continued, and four days later he developed headache and stiffness of the neck. During examination on the following day projectile vomiting occurred. There was marked stiffness of the neck, and Kernig's sign was strongly positive. The left knee-jerk was brisker than the right, the right ankle-jerk being absent and the left diminished. No other abnormalities were found. The blood-pressure was 150/90. Lumbar puncture gave a uniformly blood-stained fluid under a pressure of 140 mm. The supernatant fluid was brown. There were

225,000 red blood-cells and 3,800 white cells (mainly degenerate polymorphs) per c.mm., and the protein content was 240 mg. per 100 ml. Plain X-rays of the spine were normal. He recovered in five weeks, convalescence being complicated by an attack of delirium tremens.

Comment. A case of spinal subarachnoid haemorrhage apparently precipitated by trauma and preceded by root pain. Cerebral symptoms were mild, and did not develop until four days after the onset of the *coup de poignard*. The cause was undetermined. The alteration in the tendon-reflexes may have been due to pre-existent alcoholic polyneuritis or to the haemorrhage.

Case 2. A girl aged 11 years, admitted February 3, 1948 (L.H. No. 22481/51). Four months previously she suddenly had severe lumbar pain radiating to the right leg. She was provided with a plaster jacket, and gradually recovered. Ten days before admission the pain returned, later radiating to both thighs, and becoming so severe that she was unable to walk. On examination she was a drowsy, irritable girl, with extreme head-retraction and opisthotonos. She lay on her side with the hips and knees flexed. No other abnormalities were found. Immediate lumbar puncture yielded a heavily blood-stained fluid. There was no block. Plain X-rays of the spine showed spina bifida occulta of D 11 and 12. Lumbar puncture one week later provided a yellow fluid containing 19 cells per c.mm. and 300 mg. protein per 100 ml. She recovered gradually in five weeks. Lumbar myelography was then performed; the cerebrospinal fluid was clear and colourless, containing 17 cells per c.mm. and 60 mg. protein per 100 ml. The oil injected broke up into globules, which were retained in the lumbar sac and could not be made to run above the level of D 12. She remained well until April 1953 (age 16 years), when she awoke one morning with lumbar pain and back stiffness. On examination three weeks later the pain had almost gone, and the only abnormal sign was limitation of straight-leg raising to 40° on both sides. X-rays of the spine showed no further change. One year later she was well, apart from occasional mild backache, and there were no abnormal signs save that the tendon-reflexes in her legs were much brisker than those in the upper limbs.

Comment. This patient suffered three attacks of spinal subarachnoid haemorrhage, the second of which was severe and produced a picture of extreme spinal meningeal irritation. The cause of the bleeding was not established, but a spinal angioma is suspected in view of the course of the illness, the slight pyramidal signs, and the presence of spina bifida at an unusual level.

When the bleeding originates in the cervical region, headache and neck pain are predominant; this feature may make the differentiation from intracranial subarachnoid haemorrhage difficult, if not impossible, on clinical grounds alone.

Case 3. A man aged 51 years, admitted April 28, 1953 (L.H. No. 13873/53). Two weeks after partial gastrectomy for chronic gastric ulcer this patient had nephritis. His blood-pressure rose from 150/90 to 210/110. Five weeks after the operation he complained of sudden severe headache and pain in the neck, and vomited several times. Extreme head-retraction was noted. Five days later lumbar puncture revealed a heavily blood-stained fluid. On the same day he had an episode of profuse haematuria. He was transferred to the London Hospital six weeks later for further investigation, as another episode of subarachnoid bleeding had occurred, with acute head-retraction. On examination he was severely confused. His head was retracted, the spine overextended,

and the hips and knees flexed. The blood-pressure had fallen to 110/80. Lumbar puncture revealed a yellow fluid containing 160 mg. protein per 100 ml. and 110 cells per c.mm. He died eight days later, after a series of generalized convulsions.

Post-mortem findings (L.H. P.M. 182/53). Summary: subarachnoid haemorrhage; aneurysm of posterior spinal artery; progressive glomerulonephritis; old operation—Billroth I partial gastrectomy.

The aneurysm, which had ruptured, was of the right posterior spinal artery, and measured 1·2 cm. × 0·7 cm. It lay between the right cerebellar tonsil and the adjacent posterolateral part of the medulla and cervical spinal cord. The wall of the aneurysm consisted of collagenous tissue. The aneurysm contained laminated thrombus. The kidneys showed evidence of progressive glomerulonephritis. Microscopic examination of the proximal penile urethra showed haemorrhage from a cavernous haemangioma.

Comment. This case of bleeding high in the cervical region was not recognized during life as an example of spinal haemorrhage. Rupture of the aneurysm may have been provoked by hypertension, which may also have caused haemorrhage from the haemangioma of the urethra. Vascular changes due to the nephritis may have been an additional factor.

Case 4. A boy aged 15 years, admitted May 8, 1953 (L.H. No. 44798/52). This boy was born with a left forequarter cutaneous haemangioma. He had acute nephritis at the age of nine years. Ankylosis of his left elbow, with secondary wasting of the muscles, had followed several attacks of osteomyelitis. Two years before admission he suddenly developed severe pain in the neck. Investigation elsewhere showed that he had had a subarachnoid haemorrhage. He made a full recovery. One day before admission he was seized by headache and vomiting while riding his bicycle. He was taken home to bed. Retention of urine followed. On examination the head was retracted, and Kernig's sign was strongly positive. There was a faint but extensive cutaneous haemangioma involving the left upper limb and thorax. The abdominal responses were diminished on the left side, and both plantar responses were extensor. No other abnormalities were found. The blood-pressure was 105/65. Urine was voided naturally in hospital. Lumbar puncture disclosed blood-stained fluid under a pressure of 180 mm. There was complete spinal block. The supernatant fluid contained 500 mg. protein per 100 ml. Vertebral angiography revealed a vascular malformation of the cervical spinal cord. On May 20, 1953 an extensive angioma, involving the first four cervical segments of the cord, was displayed at operation by Mr. D. W. C. Northfield. The patient was treated with a course of deep X-rays. Recovery was complete, and he has remained well. The nervous system is now normal on examination, apart from the muscular wasting previously noted in the left upper limb.

Comment. The cutaneous vascular abnormality naturally suggested the possibility of a spinal vascular anomaly as the source of bleeding. The episode of urinary retention was considered suggestive of a spinal lesion; otherwise the symptoms of haemorrhage from this high cervical lesion would have equally well suggested an intracranial subarachnoid haemorrhage.

2. *Symptoms and signs of intracranial extension of the haemorrhage.* All our patients had symptoms of intracranial extension of the haemorrhage. These naturally followed very rapidly when the haemorrhage was in the cervical

region; indeed, as we have just shown, such symptoms may be the first. When the spinal haemorrhage was at a lower level, intracranial symptoms supervened after a time varying from an hour or so to several days. In our experience, the more severe the haemorrhage, the more quickly do cerebral symptoms appear. Thus the first patient, with a relatively mild haemorrhage, did not develop headache and vomiting until four days after its occurrence. Cases 5 and 6, reported below, were very severe; in both the early onset of cerebral symptoms and signs, especially altered consciousness, made diagnosis difficult in the acute stage.

Case 5. A man aged 47 years, admitted August 21, 1953 (M.V.H. No. 29800). Four years previously he developed low back pain and bilateral sciatica. Numbness appeared in the buttocks, spreading to the legs and feet. The symptoms continued with varying intensity, but had grown progressively worse in the last year. He had had difficulty in starting micturition for two months. On August 14, 1953, he was found on the floor at 4.30 a.m., and said that his legs were paralysed. A few hours later he vomited, and complained of severe headache. He was unable to pass urine, and was admitted to Whipps Cross Hospital on August 16 on this account. Examination showed a confused patient, with signs of meningeal irritation and a bladder enlarged to the umbilicus. Lumbar puncture yielded a fluid which was 'almost pure blood'. Forty ounces of urine were withdrawn by catheter. Examination on August 21 (R. A. H.) showed a patient so confused as to be inaccessible. The head was retracted, opisthotonos was present, and Kernig's sign was strongly positive. There was bilateral papilloedema (right more than left), bilateral sixth-nerve palsy, and coarse nystagmus. The right upper limb was ataxic. Both lower limbs were hypotonic and weak. The right knee-jerk was brisker than the left. Both ankle-jerks and plantar responses were absent. Sensory testing was impossible. The blood-pressure was 165/95. No other abnormalities were found. He was transferred to Maida Vale Hospital the same day, with a provisional diagnosis of brain-stem and spinal angiomas and subarachnoid haemorrhage. On arrival he complained of severe headache and backache. Bulbar palsy followed, so that in a few hours his voice became hoarse, and he was only able to swallow sips of fluid. Lumbar puncture yielded fresh blood, the fluid clotting in the manometer; the pressure was 300 mm. The next day a right third-nerve palsy appeared. Right carotid and vertebral angiography, and ventriculography, showed no evidence of an intracranial lesion. The ventricular fluid was only slightly blood-stained, containing 5,000 red cells per c.mm., but the pressure was high (350 mm.). His condition deteriorated in spite of ventricular tapping and drainage. He died on September 1, 1953 after a further episode of spinal haemorrhage.

Post-mortem findings (M.V.H. P.M. 114). Summary: massive lumbar subarachnoid haemorrhage from vascular hamartoma; acute cystitis and bilateral pyelonephritis; confluent bronchopneumonia of right upper lobe.

The spina dura mater was grossly distended in the lumbosacral and dorsal region up to the level of D 4. When the meninges were opened, a large mass of dark fluid blood and blood-clot was found, which filled the lumbar sac, gradually diminishing to the level of D 4. Above this point the cerebrospinal fluid was blood-stained both in the cervical region and within the cranium, but there was no more clot. After part of the clot had been removed, a large vascular hamartoma (angioma) was found lying behind the conus and between the nerve roots of the cauda equina.

Examination of the brain and spinal cord after fixation. No abnormality was found in the brain, brain-stem, cerebral blood-vessels, or cerebral meninges. In the spinal cord an angiomatous malformation was found extending from the conus medullaris to the level of D 6. The abnormal vessels were largest at the conus, diminishing in size towards the upper limit of the hamartoma. There was abundant blood-clot in the lumbosacral region, the haemorrhage having occurred from a large varix (Plate 5, Figs. 1 and 2). Sections of the spinal cord showed that there had been no bleeding into the substance of the cord, and that the angioma was entirely extramedullary.

Comment. The extensive cranial-nerve palsies, nystagmus, and ataxia made precise diagnosis very difficult, especially as the previous history was not available at the outset. In the absence of any intracranial lesion it must be assumed that the cerebral symptoms and signs were due to increased intracranial pressure and the relatively slight intracranial extension of the bleeding.

Case 6. A woman, aged 56 years, admitted May 17, 1954 (M.V.H. No. 31379). On January 6, 1954 she developed herpes zoster affecting the right sixth thoracic dermatome. As she entered the gate of her house on January 25 she was seized by a sudden severe pain in the back and weakness in the legs, so that she fell to the ground. She crawled up the pathway to the door, and was carried to bed. The pain spread to her head and neck, and she vomited frequently. During the next three days she became increasingly confused, and was admitted to hospital after a generalized convulsion. Examination showed marked head-retraction and opisthotonos. She was severely confused, and completely disorientated. There was bilateral papilloedema, and both plantar responses were extensor. The blood-pressure was 180/100. Lumbar puncture showed a uniformly blood-stained fluid under a pressure of 260 mm. She gradually recovered during the next few weeks. When seen by one of us (R. A. H.) in consultation on April 14, she had no complaints; her optic disks were blurred, the tendon-reflexes were exaggerated in the lower limbs, and both plantar responses were extensor. On admission to Maida Vale Hospital on May 17 she said she was completely well. The nasal edges of both optic disks were still blurred, and the tendon-reflexes in the legs were exaggerated, with ill-sustained ankle-clonus. The plantar responses were now flexor. No other abnormalities were found. Plain X-rays of the skull and spine were normal. Lumbar puncture revealed a yellow fluid under a pressure of 170 mm. There was complete spinal block. The fluid contained seven lymphocytes per c.mm., and 300 mg. protein per 100 ml. Lumbar myelography showed a complete block, with an irregular margin, at L 1 (Plate 5, Fig. 3). Cisternal myelography demonstrated a complete block at D 5, again of an irregular appearance (Plate 5, Fig. 4). She was discharged on June 4, 1954, and remains well.

Comment. In this case of spinal haemorrhage the early onset of headache, vomiting, and mental disturbances, and a major convulsion, obscured the origin of the bleeding. When the history was taken after her recovery the true sequence of events was appreciated. The attack of herpes zoster was presumably symptomatic. The lesion, in view of its length as shown by myelography and the paucity of permanent signs of spinal disorder, is probably an angioma. The irregular appearance of the spinal block may well be due to organized blood-clot and arachnoidal adhesions.

Conclusion. Headache, vomiting, photophobia, and disturbances of con-

sciousness naturally follow intracranial extension of spinal bleeding, their severity depending on the degree of haemorrhage. With massive haemorrhage more striking and widespread signs may arise, including papilloedema, extensive cranial-nerve palsies, ataxia, and major convulsions. The rapidity of onset of these symptoms, and also their nature, may easily lead to a mistaken diagnosis of intracranial subarachnoid haemorrhage.

3. *Symptoms and signs due to involvement of the spinal cord and nerve-roots.* Haematorrhachis may be accompanied by haematomyelia, in which case there may be serious disturbance of spinal-cord function. We judge that none of our patients had haematomyelia. Apart from this mechanism, the spinal cord and nerve-roots may be compressed by blood or blood-clot, or both. Organization of blood-clot may be responsible for continued compression long after the haemorrhage (Robertson, 1938), or arachnoidal adhesions may operate in a similar way (Harris, 1911). Spinal-cord signs have been slight in our patients, in spite of the size of the causal lesions (Cases 4 and 6) and the severity of the haemorrhage (Cases 2, 3, 4, and 6). In Case 4 there were bilateral extensor plantar responses and transient retention of urine. In Case 6 mild bilateral pyramidal signs were present in the lower limbs, and to a lesser degree in Case 2. In Case 5 there was severe flaccid paraplegia, due to compression of the cauda equina and the lower part of the cord. The remaining three patients (Cases 1, 3, and 7) had no signs of spinal-cord malfunction. Symptoms of root involvement included root pains, as already described. Diminution of the tendon-reflexes in the legs was surprisingly infrequent.

Spinal Subarachnoid Haemorrhage in Polyarteritis Nodosa

It is well recognized that intracranial subarachnoid haemorrhage may occur in polyarteritis nodosa (Foster and Malamud, 1941; Logue and Mullins, 1946; Summers, 1950); spinal haemorrhage does not seem to have been reported. One of our patients (Case 7) may have been suffering from polyarteritis nodosa, though the diagnosis was unproved. Two certain examples of spinal subarachnoid bleeding in polyarteritis nodosa have been found in the records of the Bernhard Baron Institute of Pathology (Cases 8 and 9).

Case 7. A man aged 41 years, admitted October 19, 1953 (L.H. No. 37341/53). For many years he had been liable to attacks of sinusitis, which had often been treated with sulphonamides. Three years previously he had been refused life insurance on account of obesity and hypertension (blood-pressure 160/100). Four weeks after admission he had a sore throat. He was treated with 'sulphatriad' (total dosage 42 gm.). Eleven days before admission he developed oedema of the eyelids, and the urine was found to contain much albumin and, on microscopy, many red cells; the blood-pressure was 190/120. He was treated with a diet of orange juice, and the oedema disappeared. Five days before admission he experienced sudden, agonizing pain in both buttocks, radiating to the thighs. Gross haematuria and epistaxis followed. Examination on admission showed petechial haemorrhages on the hard palate, and several small ecchymoses on the legs. There was no oedema of the legs. The blood-pressure was 190/130. There was head-retraction, and gross spinal rigidity. Kernig's

sign was strongly positive. The edges of both optic disks were slightly blurred, and a small patch of exudate was seen in the left fundus. The nervous system was normal. Lumbar puncture revealed a grossly blood-stained fluid. Examination of the blood showed: haemoglobin, 78 per cent.; white cells, 12,000 per c.mm. (69 per cent. polymorphs); erythrocyte sedimentation rate, 100 mm. in one hour; plasma-proteins, 8·1 gm. per 100 ml. (albumin 3·7 gm., globulin 4·4 gm.); blood-urea, 87 mg. per 100 ml. The bleeding time was more than 15 minutes. The urine contained a high concentration of albumin, a few red and white cells, and a few granular and hyaline casts.

He was treated with a fluid diet and aureomycin. During the first week in hospital there was some degree of mental confusion, especially at night. The signs of spinal meningeal irritation slowly subsided. A crop of purpuric spots appeared on his right arm one day after the taking of his blood-pressure. He made a complete recovery from his subarachnoid haemorrhage in three weeks, but remained in hospital just over three months because of his renal disease. After six weeks an arthritis of the right metatarso-phalangeal joint developed. The blood uric acid was 7·5 mg. per 100 ml. His blood-pressure returned to its previous level. One year after the onset of his illness he was well, apart from symptoms referable to his chronic sinusitis. His urine occasionally contained a trace of albumin. The plasma-protein was 7·5 gm. per 100 ml. (4·8 gm. albumin, 2·7 gm. globulin), blood-urea 42 gm. per 100 ml., blood uric acid 6·8 mg. per 100 ml., and erythrocyte sedimentation rate 18 mm. in one hour.

Comment. The collective diagnosis of polyarteritis nodosa would best explain this case of nephritis, purpura, and spinal haemorrhage following a sore throat treated with sulphonamide. The extremely benign course, and particularly the resolution of the nephropathy, are points against the diagnosis. The hypertension might have precipitated haemorrhage from a pre-existent spinal vascular anomaly. In view of the persistence of increased blood uric acid, after the return to almost normal renal function, it is likely that the arthropathy was due to gout.

Case 8. A man aged 39 years, admitted December 5, 1943 (L.H. No. 31137). During the fortnight preceding admission he had progressively developed pains in many joints, purple spots on one foot, gross haematuria, and severe dyspnoea. He had previously been treated surgically for papilloma of the bladder. On examination he was pale and sweating; temperature 101° F., pulse 110, and respirations 24. All his joints were painful on movement. A systolic murmur was heard all over the praecordium. The blood pressure was 170/95. Five days after admission he complained of severe headache, photophobia, and pain between the shoulder blades. On examination there was neck rigidity, and a positive Kernig's sign. The knee- and ankle-jerks had become sluggish. Lumbar puncture yielded blood-stained fluid. He died in convulsions four days later.

Post-mortem findings (L.H. P.M. 237/1943). Summary: melaena; ulcers in the intestines; slight meningeal haemorrhage; polyarteritis nodosa.

There was slight haemorrhage in the leptomeninges over the occipital poles, and very slight bleeding in the posterior parietal regions and over the vermis and posterior border of the cerebellum. No abnormality was found in the substance of the brain or cerebellum, or in the arteries of the base. There was slight subarachnoid haemorrhage all over the thoracic cord and the lower part of the cauda equina. The sources of haemorrhage were an artery running with the eighth right posterior cervical root, and another small vessel on the posterior

aspect of the cord at the 10th thoracic level. A section of the artery associated with the eighth cervical root shows the usual changes seen in polyarteritis nodosa. No abnormality was noted in the substance of the spinal cord. The large intestine contained thick tarry blood, evidently deriving from numerous small superficial ulcers found in the ileum and jejunum.

Case 9. A woman aged 69 years, admitted June 10, 1931 (L.H. No. 40893). She had had 'heart trouble' for many years. Three days before admission she had abdominal pain followed by vomiting. For one day she had been unable to move her legs. On examination she was moribund, although conscious. The nervous system was normal apart from the lower limbs. She had a complete flaccid paraplegia, with loss of the knee- and ankle-jerks and plantar responses.

Post-mortem findings (L.H. P.M. 273/31). Summary: subarachnoid haemorrhage in the spinal canal; disseminated polyarteritis nodosa acuta.

There was great recent haemorrhage in the subarachnoid space from D 6 downwards, this part of the cord and the cauda equina being completely enclosed in a layer of gelatinous clot, 0·5 to 0·8 cm. thick. Several bleeding points were discovered; these were all small aneurysms on arteries associated with dorsal, lumbar, and sacral posterior roots. The spinal cord itself showed no abnormality. There was also an area of considerable haemorrhage, up to 0·2 cm. thick, in the leptomeninges over the right occipital pole; no bleeding point was discovered here. Haemorrhages were also present in the subcutaneous tissues, muscles, kidney, spleen, pancreas, endometrium, bladder, intestinal wall, and liver. Ante-mortem thrombi had formed in many visceral arteries; haemorrhages were seen in the walls of these vessels. Microscopic examination of the affected arteries shows the changes characteristic of polyarteritis nodosa.

Comment. There was intracranial and spinal subarachnoid haemorrhage in both Cases 8 and 9. In Case 9 the spinal bleeding had been great, leading to flaccid paraplegia. Haemorrhage into the affected spinal roots also contributed to the paralysis. The bleeding in Case 8 was relatively minor in degree, and in this patient it is difficult to separate the symptoms and signs due to the different haemorrhages; the severe interscapular pain may, however, have been a *coup de poignard.*

Pathology

The source of haemorrhage was certainly determined in three of our seven patients. Two (Cases 4 and 5) had vascular hamartomas (spinal angiomas), and one (Case 2) an aneurysm of the posterior spinal artery. It is probable that another patient (Case 6) has an angioma, and this is also the likely diagnosis in Case 2. The cause remains problematic in Cases 1 and 7. We have suggested that one patient (Case 7) had polyarteritis nodosa, although this diagnosis is hazardous, and in Case 1 the probability is that the patient has an angioma. Of the five examples of spontaneous haematorrhachis discovered in the records of the Bernhard Baron Institute, two (Cases 8 and 9) occurred in patients with polyarteritis nodosa. The third patient was a baby who died at the age of 24 days (L.H. P.M. 419/27). She had spina bifida and a meningocele. Here the bleeding was due to the rupture of a mycotic aneurysm on a vessel in the lumbar sac. Of the two other patients one, a woman aged 20 years, died from encephalitis lethargica (L.H. P.M. 52/21), and the other, a woman aged 28 years, from

diabetes mellitus (L.H. P.M. 536/26). In neither case did the clinical notes give any record of an episode resembling spinal haemorrhage, nor did examination of the sections available show the source of the bleeding. A study of the recorded cases suggests that spinal angiomas are undoubtedly the commonest cause of spinal subarachnoid haemorrhage. Nevertheless haematorrhachis is not a common symptom of the condition. Sargent (1925), Globus and Doshay (1929), Epstein, Beller, and Cohen (1949), and Brion, Netsky, and Zimmerman (1952) have published series of four, four, six, and nine cases of spinal vascular anomalies respectively, all without subarachnoid haemorrhage. On the other hand Trupp and Sachs (1948) had three examples of haemorrhage among their seven patients. In a personal series (R. A. H.) of seven patients with proved spinal angiomas, two have suffered subarachnoid haemorrhage. Haematomyelia and haematorrhachis may occur together (Wyburn-Mason, 1943, and others) but they are frequently divorced. None of our cases had haematomyelia, and this circumstance no doubt is largely responsible for the full recovery in the five survivors. Haemorrhage from angiomas may be precipitated by trauma (Harris, 1911; Brion, Netsky, and Zimmerman, 1952), and perhaps by parturition (Thiebaut and Schneeberger Ataide, 1951). Trauma apparently provoked haemorrhage in our Case 1, but here the cause of bleeding was not established. Arterial hypertension might be another precipitating factor, though we have no experience on this point. The bleeding in the cases of polyarteritis nodosa came from radicular arteries involved in the generalized vascular disease. Aneurysm (Case 3) forms the only other pathological condition which we have encountered. Here the bleeding was probably precipitated by renal hypertension. The aneurysm was so disorganized by its rupture that we can hazard no opinion as to its nature. We have no examples of spinal bleeding from primary or secondary tumours.

Diagnosis

The diagnosis of any form of subarachnoid haemorrhage rests ultimately on the demonstration of blood-stained cerebrospinal fluid at lumbar puncture. The clinical recognition of the spinal variety may be extremely difficult. The complaint of sudden, intense backache, perhaps accompanied or followed by root pains, may be made by patients with herniated intervertebral disks, vertebral collapse, spinal infections, including pyogenic and tuberculous conditions, spinal thrombosis, haematomyelia, and dissecting aneurysm, to mention but a few disorders. Generally, however, the picture of spinal meningeal irritation which our patients presented is also shown only by patients with spinal meningitis, including extradural abscess. The absence of fever and other signs of infection are differentiating points. The final answer lies with lumbar puncture. This procedure may be a matter of difficulty because of spinal rigidity or opisthotonos, especially in a child, but in all our patients satisfactory punctures were made. The collection of the cerebrospinal fluid in three tubes is a great help in distinguishing subarachnoid haemorrhage from trauma caused by the needle (McMenemey, 1954). When the haemorrhage is less intense, the

distinction from an acute disk herniation or vertebral disease may be difficult. Case 1 exemplifies this point. Here the development of headache and vomiting, in a patient suffering from sudden backache and bilateral sciatica, led an orthopaedic colleague to lumbar puncture and the correct diagnosis. It is axiomatic, however, that a patient with bilateral sciatica should undergo lumbar puncture and examination of the spinal fluid. No doubt occasional patients, with small haemorrhages, are thought to be suffering from lumbago or sciatica due to disk lesions, and recover without the true diagnosis being made. The third haemorrhage in Case 2 might easily have been dismissed in this fashion.

The differentiation of spinal and intracranial subarachnoid haemorrhage. It is well recognized that low backache and sciatica may occur in intracranial subarachnoid haemorrhage, as the result of the leakage of blood into the spinal subarachnoid space. This is particularly liable to happen when the patient remains ambulant. Nevertheless it is advisable to consider the spinal canal as the site of bleeding when the first symptoms are backache or sciatica, headache and vomiting following later. If, on the other hand, the first symptom is headache, the bleeding should be either intracranial or in the cervical spinal canal. The combination of sudden backache and root pain with signs of spinal meningeal irritation is, in our experience, pathognomonic of the spinal variety of haemorrhage. The main difficulty arises in those patients who rapidly develop cerebral symptoms and signs, so that the clinical picture is clouded, for example Cases 5 and 6. Such patients may be unable to give a history. Here the presence of intense spinal meningeal irritation or signs of a spinal-cord lesion may afford valuable clues. Michon (1928) considered that the persistence of backache and sciatica, when the cerebral symptoms have cleared, is indicative of a spinal source for the haemorrhage. The history given by relatives may be helpful, for example Case 5. The patient may be able to give the true history in convalescence, as in Case 6. A further complication which needs consideration in certain patients is the occurrence of multiple vascular abnormalities. Brion, Netsky, and Zimmerman (1952) had a patient with paraplegia caused by a spinal angioma, but death was caused by massive haemorrhage from an aneurysm of the right posterior communicating artery. Multiple angiomata are sometimes present in the nervous system, though this is rare. Lastly, haemorrhages can obviously be widespread in polyarteritis nodosa, as in Cases 8 and 9, though the predominant lesion may be cerebral or spinal.

Diagnosis of the cause of the spinal haemorrhage. 1. *Angioma.* It is now accepted that these vascular lesions are hamartomas. Other congenital abnormalities may be found in association with angiomas, and their presence would suggest an angioma as the cause of bleeding. Cutaneous vascular naevi may accompany spinal angiomas (Cobb, 1915; Silverman, 1945–6). These cutaneous lesions, however, do not always correspond with the level of the spinal lesion, nor are they associated with any special kind of vascular malformation; for example, Johnston (1938) reported the case of a boy with a cutaneous vascular naevus and an epidural haemangioblastoma. The extensive cutaneous naevus

in our Case 4 was a correct indication of the type of spinal lesion. Multiple pigmented, non-vascular naevi, multiple lipomata, and spina bifida occulta have also been described in association with spinal vascular malformations. In the clinical history a story of progressive disturbance of function affecting the cord or cauda equina, especially if episodic in type, will suggest angioma. Incidentally, auscultation of the spine was negative in all our patients. Lastly, angioma appears to be the commonest cause of spontaneous haematorrhachis. Complete recovery from the bleeding, without residual signs, is no contra-indication to the diagnosis (Case 4, and probably Case 6). Investigations, in particular the special radiological techniques, may be helpful. Thus lumbar puncture performed several weeks after the ictus may reveal some degree of spinal block, and yield a fluid containing an excess of protein. Lumbar puncture is not without risk in a patient who has an angioma in the lumbar sac; the abnormal large vessels could be damaged by the needle; this may have happened in Case 5, though we have no direct evidence on the point. The large vessels in an angioma may be outlined by the contrast substance at myelography (Bull, 1951). Major degrees of block may result especially from the organization of blood-clot and the formation of arachnoidal adhesions, if our interpretation of the myelographic studies in Case 6 is correct.

2. *Aneurysm.* It is unlikely that this diagnosis will be successfully achieved in life. Such lesions are very rare in the spinal canal.

3. *Neoplasm.* From Fincher's (1951) account it appears that haemorrhage from spinal neoplasms is much less brisk than that from the angiomas. Ependymomas in the lumbar sac are the commonest spinal neoplasms to bleed, so far as we can determine. The spinal capillary haemangioblastomas, which are rare, are worth mentioning; in view of their connexion with the pia they might be a cause of subarachnoid haemorrhage. In the absence of other symptoms or signs, diagnosis can be made on the examination of the spinal fluid and myelographic appearances.

4. *Polyarteritis nodosa.* This diagnosis will be suggested when other evidence of the condition is found on clinical examination. There seems to be no reason why spinal bleeding should not be the initial symptom on rare occasions.

5. *Blood dyscrasias.* Walton (1953) has recently enumerated the various blood diseases in which subarachnoid haemorrhage may occur. We have concluded from our researches in the literature that these diseases must be a rare cause of massive spinal subarachnoid bleeding. Full examination of the blood, and if necessary of the bone-marrow, should establish the diagnosis in such cases. Recently Yuhl (1955) reported a patient who suffered spontaneous epidural, subdural, and subarachnoid spinal haemorrhage while under treatment with dicoumarol.

6. *Generalized toxi-infective conditions.* The occurrence of spinal haemorrhage in the course of typhoid fever has already been mentioned. It is conceivable that bleeding might take place from the rupture of a mycotic aneurysm, as in the case we have quoted of a baby who had an infected meningocele.

Course and Prognosis

This will clearly depend upon the degree of haemorrhage and the underlying cause. Two of our seven patients died. The other five made total recoveries in a matter of a few weeks or months, though two of them had severe haemorrhages (Cases 2 and 6). In Case 2 there were two recurrences, and in Case 4 one. It appears that frequent recurrences are more likely to ensue when the cause is a neoplasm (Fincher, 1951). The good recovery in our patients is undoubtedly linked with the fact that not one of them had haematomyelia. Cerebral atrophy with ventricular dilatation is well recognized as a sequel of severe and recurrent intracranial subarachnoid haemorrhage. The possibility of similar permanent cerebral changes following spinal subarachnoid haemorrhage is raised by the finding of ventricular dilatation in Abbott's (1939) patient, who had more than 25 spinal haemorrhages from an ependymoma of the filum terminale. No cause for this hydrocephalus was found, although Abbott suggested that basal arachnoid adhesions might have been present.

Treatment

All our patients were treated conservatively except one (Case 4), and here surgical intervention was limited to an exploration of the cervical spine. We are unable from experience with our patients to assess the value of lumbar puncture as a therapeutic measure; we are of opinion, however, that with massive, life-threatening haemorrhage this procedure is of no assistance. We also find it difficult to judge whether removal of blood by lumbar puncture aids in the prevention of clot-organization and formation of adhesions in patients who have less severe degrees of bleeding; it may well do so. The withdrawal of spinal fluid had no harmful effect in our patients, except possibly in Case 5. If diagnostic lumbar puncture is followed by symptomatic improvement, it is reasonable to repeat it as a therapeutic procedure. In view of the unexpectedly benign course of the illness in most of our patients, our inclination has been to leave well alone. Treatment has therefore been symptomatic. Surgical aid will naturally be sought when the spinal lesion is neoplastic. Surgery also has a place in the treatment of spinal compression by organized blood-clot or arachnoidal adhesions (Harris, 1911) but, in view of the complete recovery of our only patient to suffer this complication (Case 6), we did not adopt this form of treatment. It does not appear that surgical intervention could achieve any success in dealing with the gross haemorrhage seen in some patients, as in Case 5. In our experience the results of deep X-ray treatment of spinal angiomas have been disappointing. In view of the fact that labour may precipitate haemorrhage from a spinal angioma (Thiebaut and Schneeberger Ataide, 1951), planned caesarean section should be considered as a prophylactic measure. We intend to advise the young woman (Case 2) accordingly at the appropriate time.

We are grateful to our colleagues who have permitted us to report their patients, and to Professor Dorothy Russell for access to the records of the Bernhard Baron Institute of Pathology and for the post-mortem reports on

Cases 3, 8, and 9. Dr. C. E. Lumsden kindly provided the post-mortem report on Case 5.

Summary

A series of seven cases of spinal subarachnoid haemorrhage is reported. The clinical picture is described and discussed. The difficulty in differentiating the condition from its intracranial counterpart is emphasized.

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Figs. 1 and 2. Case 5. Views of the lumbar enlargement and cauda equina, to show the spinal angioma and blood-clot in the lumbar sac

Fig. 3. Case 6. Lumbar myelogram showing complete block at L1

Fig. 4. Case 6. Cisternal myelogram showing complete block at D 5

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RADIATION REACTIONS IN THE LUNG[1]

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With Plates 6 to 11

It is well recognized that the margin between a dose of X-rays that is therapeutically effective and one that produces undesirable damage to adjacent healthy tissue is always small, and often non-existent. Nevertheless it is rare to see such damage in serious or lethal degree. The hazard to bone-marrow is so well known that examination of the peripheral blood at frequent intervals during radiotherapy is routine practice, and such measures make anything more than transient depression of haemopoiesis a rarity. The sterilizing potentialities of radiotherapy in female sufferers from ankylosing spondylitis have long been recognized, and techniques have been developed to avoid what was once accepted as a necessary price of effective treatment. The damage which X-rays may do to healthy kidneys, during wide-field irradiation of the abdominal glands after removal of seminomas, has been fully described by Kunkler, Farr, and Luxton (1952) and Luxton (1953), and special precautions are now taken to protect the kidneys. Another tissue which may occasionally suffer at the hands of the radiotherapist is the lung. The occurrence of such damage was first described by Groover, Christie, and Merritt in 1922, and in the early days of radiotherapy it must have been relatively common; McIntosh and Spitz (1939) found radiological evidence of the pulmonary effects of radiation in 36 of 60 patients who were given radiotherapy for carcinoma of the breast, while Widmann (1942) reported 62 patients out of 273, and Leach, Farrow, Foote, and Wawro (1942) 77 out of 347, as showing damage to the lungs after deep X-ray therapy for breast cancer. Engelstad (1940) gave the incidence as 5·4 per cent. for carcinomata of the breast, and 20·4 per cent. for irradiated oesophageal neoplasms; Warren and Spencer (1940) found histological evidence of radiation effects in the lung in 28 of a total of 234 autopsies performed on patients who had been given radiotherapy. Today such effects are uncommon, but the advent of the atomic age greatly enhances their importance, and justifies a review of the condition as it is seen in current medical and radiotherapeutic practice. The magnitude which the problem might assume is reflected in the reports of Tullis (1949) on the lungs of swine which died as a result of the atom-bomb explosion at Bikini in 1946, and of Liebow, Warren, and DeCoursey (1949)

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on the lungs of human beings who died as a result of the Hiroshima and Nagasaki atom bomb explosions in August 1945.

The Present Investigation

Patients. The present communication is based on a study of 29 patients with radiation damage to the lungs, all of whom were seen at the United Birmingham Hospitals during the past five years. The primary diseases for which they were given radiotherapy are shown in Table I; the details of treatment in each case, and a note on the radiotherapeutic technique employed, are given in the Appendix. The mean age was 45·9 years (range 18 to 79 years). The sex distribution of 22 female to seven male patients is wholly due to the fact that radiation damage to the lungs is most frequently seen after radiotherapy for breast cancer. If this group is excluded, the sex distribution is predominantly male (seven to five). As a group, the 29 patients were significantly under-weight ($P < 0{\cdot}01$) as compared with the average weight of healthy people of the same sex, age, and height (Davenport, 1923; Kemsley, 1951–2). Apart from their initial malignant conditions, only five had any other significant disease. One patient (Case 1) had a severe iron-deficiency anaemia, one (Case 6) had disseminated sclerosis, one (Case 7) had diabetes and mild hypertension, and two other patients (Cases 4 and 26) also had a moderate degree of benign essential hypertension.

TABLE I

Initial Diagnosis in 29 Cases

Breast carcinoma	17
Reticuloses	7
Thyroid carcinoma	3
Carcinoma of oesophagus	1
Carcinoma of bronchus	1

Symptoms and signs. The interval between the conclusion of radiotherapy and the onset of symptoms was known in 21 cases, and is shown in Fig. 1. It will be seen that in some cases it was as short as two weeks, and in others as long as four months; but in the majority of cases symptoms developed during the earlier weeks of this period. Two of the 29 patients (Cases 6 and 9) never had any symptoms, the lung damage coming to light on routine follow-up radiography. Both these patients had received radiotherapy through routine breast fields after mastectomy for carcinoma, and the degree of lung damage was slight. In a third patient (Case 29) the radiation damage to the lung was only detected when carcinomatosis developed. A 'chest cold' may have represented the pneumonitis stage, but may have been unconnected with radiation, as the patient had a bronchitic tendency. In the remaining 26 patients dyspnoea was the dominant symptom (Fig. 2). At first noticeable only on exertion, it increased in severity, and in severe cases became evident at rest. If the patient survived after dyspnoea reached its peak, it gradually receded, but only in the mildest cases was a normal exercise tolerance ever restored. In fatal cases the speed of

deterioration was sometimes extremely rapid. Two patients (Cases 17 and 18) died from respiratory insufficiency within one week of walking into the out-patient department. Sixteen of the patients also had a dry, irritating cough. Exertion and deep breathing seemed to provoke the cough which, like the

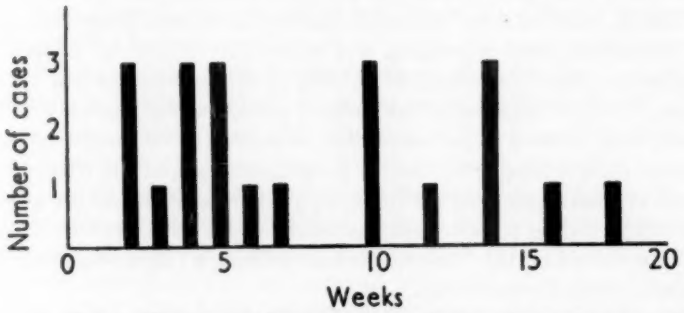

FIG. 1. The interval between the conclusion of radiotherapy and the onset of symptoms of radiation pneumonitis.

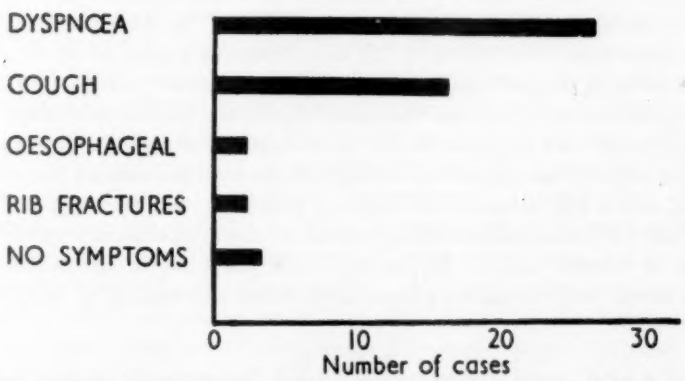

FIG. 2. Relative frequency of different symptoms in the group of 29 cases.

dyspnoea, became increasingly troublesome for a few weeks, and then gradually improved. In two of the patients it disappeared after a few weeks, but in the remaining 10 who survived it persisted indefinitely. Two patients (Cases 2 and 21) had severe pain from fractured ribs. In neither case was the cause of the pain apparent until a chest radiograph was carefully scrutinized. Two other patients were troubled by oesophageal symptoms. One (Case 4), after post-operative radiotherapy for carcinoma of the breast, complained of a feeling of tightness on swallowing, and of the regurgitation of unaltered food. Barium studies showed irregularity of the oesophageal outline, and oesophagoscopy showed mucosal changes throughout the length of the oesophagus; 2 cm. of gastric mucosa were in the chest, the cardia having apparently been pulled upwards by fibrotic changes in the oesophagus. The other patient (Case 19), after supervoltage radiotherapy for a carcinoma of the oesophagus, developed regurgitation

of gastric contents; a barium-swallow examination showed free oesophageal reflux, and the cardia two inches above the diaphragm.

During the pneumonitis stage conventional clinical examination has shown evidence of abnormality in only a few of the more severe cases. Even in these the percussion note and breath sounds have been normal and adventitious sounds absent, and the most noticeable features have been dyspnoea and cyanosis, a diminished chest expansion, and a peculiar 'door-stop' obstruction to full inspiration when the patient attempted to take a deep breath. As fibrosis developed, seven of the more severe cases of unilateral damage showed mediastinal shift, and dullness to percussion and alteration of the breath sounds over the affected apex or lung. Only two of the patients showed any febrile reaction. One (Case 17) had slight fever for three days before he died, and the other (Case 12) was febrile during a very violent reaction, which occurred two weeks after radiotherapy given by the large single-dose technique; this treatment had followed mastectomy for carcinoma.

Ancillary investigations. None of the patients have shown any anaemia, and in all but three instances the total and differential white-cell count was normal. The three exceptions (Cases 16, 17, and 28) were severe cases in which the whole of both lungs was involved. Two of them were fatal. The total white-cell counts in these three cases were 12,600, 10,700, and 19,000 per c.mm., about 85 per cent. of the cells being polymorphs in each patient. In the few patients in whom the erythrocyte sedimentation rate was tested during the pneumonitis stage, it was markedly raised—for example, 52 mm. in one hour (Westergren). The maximum breathing capacity and divisions of lung volume were determined in nine of the patients, and it will be seen from Table II that both were reduced, though the ratio of the various divisions of lung volume to the total capacity was much the same as in normal people. In the only case (Case 16) in which samples of arterial blood were obtained, oxygen saturation was normal at rest, but de-

TABLE II

Results of Respiratory Function Tests

Case number	*1*	*15*	*16*	*17*	*20*	*22*	*27*	*28*	*29*
Age (years)	48	38	21	30	60	26	27	18	46
Sex	F	F	M	M	F	F	F	M	F
Height (inches)	58	..	..	..	61	60	64	70	..
Weight (lb.)	79	..	..	158	157	106	140	129	..
Chest expansion (inches)	..	2	⅞	2	1½	1½	1½	1½	..
Maximum breathing capacity (l./min.)	29·5	36·6	63·5	39·0	34·0	24·0	47·0	71·4	65·0
Total capacity (l.)	..	..	2·16	..	3·39	3·33	3·17	3·39	2·56
Vital capacity (l.)	1·20	2·05	1·26	0·79	2·56	1·90	2·05	1·30	1·63
Inspiratory capacity (l.)	..	..	0·58	0·56	1·70	1·23	1·31	0·92	1·30
Expiratory reserve volume (l.)	..	..	0·68	0·23	0·86	0·66	0·74	0·38	0·33
Functional residual capacity (l.)	..	..	1·58	..	1·70	2·10	1·86	2·47	1·26
Residual volume (l.)	..	..	0·90	..	0·83	1·43	1·12	2·09	0·93
Residual volume/Total capacity (%)	..	..	42	..	24	43	35	62	36

saturation (83·3 per cent.) became evident on exercise. The carbon-dioxide content was normal at rest and on exercise.

Radiological appearances. The chest radiographs are far more helpful than physical examination in the diagnosis of radiation damage to the lung. In the pneumonitis stage the appearances, in breast cases, are those of upper-zone consolidation (Plate 6, Fig. 5); where both lungs are diffusely involved, fan-shaped shadowing is seen spreading out from both hila, as in pulmonary oedema (Plate 6, Fig. 6). Evidence of fibrosis develops rapidly in the form of pleural and pericardial tenting, and in unilateral cases mediastinal shift (Plate 6, Fig. 7), and an alteration in the character of the lung-shadowing is soon apparent. The area of skin change due to radiation accurately mirrors the extent of lung damage that will be evident radiologically (Plate 7, Fig. 8 *a*, *b*, *c*), but our clinical and histological studies have shown that the damage is far more widespread than the chest radiograph suggests, and that stray radiation has a more potent effect than is commonly supposed. Case 4 exemplifies this; the patient, after mastectomy, received radiotherapy through left internal and external glancing and left anterior and posterior axillary fields, but developed radiation damage in both lungs and severe oesophageal symptoms. Another patient (Case 12) received treatment through similar portals, and virtual destruction of the entire left lung resulted (Plate 8, Fig. 9), while in Case 29, another instance of breast carcinoma treated through the same fields, although the radiograph suggested that radiation damage was confined to the left upper zone, histological examination showed that it was present in all lobes of both lungs.

Pathology. In only three of the patients who died was it possible to obtain an autopsy. One (Case 17) has already been reported in some detail elsewhere (Whitfield, Lannigan, and Bond, 1954). He was a man of 30 years, with Hodgkin's disease involving the glands on both sides of the neck and in the right hilar and paratracheal area, who was given treatment by cervico-thoracic baths. One month after the conclusion of X-ray treatment he developed dyspnoea, and died from respiratory insufficiency five weeks later. Autopsy showed bilateral pleural effusions and firm, rubbery, airless lungs, with a thickened pleura, showing depressed irregular scars. Histologically the striking feature was a loss of alveolar space, due to a multiplicity of factors—thickening, lymphocytic infiltration, hyalinization, and fibrosis of the alveolar walls, swelling and distortion of alveolar lining cells, and the presence within alveoli of exudate, hyaline membrane, desquamated cells, and foamy macrophages. Thickening and fragmentation of the elastica, and an increase in the amount of fibrous tissue around bronchi and large vessels, were also seen (Plate 8, Figs. 10 and 11). The second autopsy was in the case of a 79-year-old man (Case 19), who died from radiation damage to the lungs six weeks after the conclusion of supervoltage X-ray therapy for carcinoma of the oesophagus. The whole of the lung tissue was firm and fibrotic, and histologically showed changes similar to those found in Case 17, but in addition there were many thin-walled abscesses, and bronchopneumonic consolidation at the bases. The third autopsy (Case 29) was that of a 46-year-old woman, who died from carcinomatosis 10 months after

mastectomy and radiotherapy for carcinoma of the left breast. Chest radiographs showed fibrosis of the left upper lobe, as well as secondary growth in both lungs. Histological examination showed carcinoma in both lungs, but in addition all lobes of both lungs showed thickening and hyalinization of alveolar walls, and in the lumen of the alveoli organizing exudate, foamy phagocytes, desquamated cells, and in places the formation of hyaline membrane (Plate 9, Figs. 12 and 13).

Treatment. There is of course no curative treatment for radiation damage to the lungs, and only symptomatic measures were employed in the milder cases.

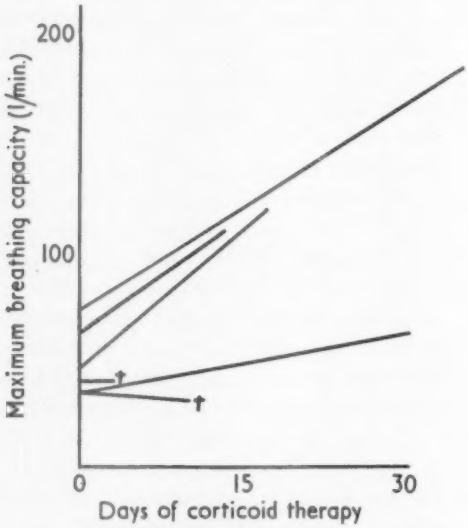

FIG. 3. Effect of corticoid therapy on the maximum breathing capacity (Cases 15, 16, 17, 20, 27, and 28).

Severely affected patients were given antibiotic cover during the pneumonitis stage in order to prevent superimposed infection, and in six of the worst cases corticoid therapy was employed (Cases 15, 16, 17, 20, 27, and 28). Four of these patients (Cases 15, 16, 27, and 28) have already been reported elsewhere (Whitfield, Bond, and Arnott, 1954). Three of them died (Cases 15, 16, and 17), but striking subjective and objective improvement resulted in the other three, and temporarily in Case 16; the maximum breathing capacity increased (Fig. 3), as did also the divisions of lung volume (Fig. 4). Case 28 exemplifies this response. The patient was given cervico-thoracic baths for lymphosarcoma involving the glands on the left side of the neck. Three weeks later he developed dyspnoea and dry cough, and when he was admitted to hospital after a further fortnight he was severely dyspnoeic at rest, his chest radiograph (Plate 10, Fig. 14) showed shadowing spreading out from both hila, and it was feared that he would die soon. After three and a half weeks of corticoid therapy he could walk up a flight of stairs without distress, and his chest X-ray (Plate 10,

Fig. 15) showed marked improvement. It is of course quite possible that the improvement which occurred in this and the other three cases would have occurred without corticoid therapy. Once the stage of fibrosis has developed, little can be done. In two severe unilateral cases Bergmann and Graham (1951)

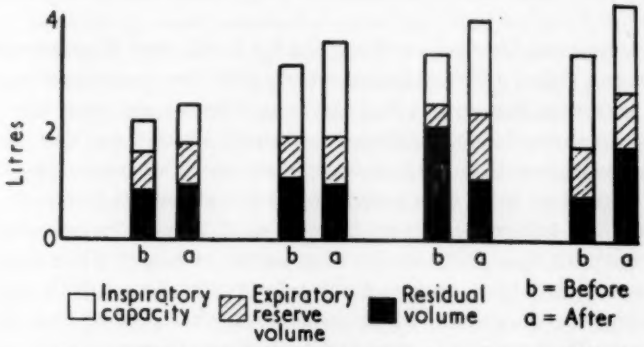

FIG. 4. Effect of corticoid therapy on lung volume (Cases 16, 20, 27, and 28).

carried out pneumonectomy, and this operation was considered in one of our patients (Case 1) who developed bronchiectasis in a severely fibrotic lung. Conservative measures, however, produced such marked improvement, and the patient was so unstable psychologically, that it was decided she would be better without operation.

Discussion

Whenever X-ray treatment is given to the thorax the lungs are at risk, and it is surprising, in view of the widespread use of radiotherapy and the relatively high dosage, that more cases of radiation damage to the lungs are not seen after irradiation of bronchial carcinomata; but the difficulties of differentiating between advancing pulmonary neoplasia and damage resulting from its radiotherapy are virtually insurmountable during life. The solitary case reported above of damage caused by X-ray treatment of an oesophageal carcinoma reflects the strong local bias towards surgical treatment of this condition. Irradiation of oesophageal growths has always been fraught with considerable danger of producing serious lung damage, in spite of the advances in technique devised by Levitt (1935) and Kaplan and Etkin (1948). In a group of patients who receive precisely similar courses of radiotherapy to the thorax for breast carcinoma or some other neoplastic state, a small percentage develop pulmonary radiation fibrosis, while in the remainder the lungs escape damage. The explanation of this selective liability is not yet fully elucidated. McIntosh (1934) and McIntosh and Spitz (1939) suggested that age and arteriosclerosis were predisposing factors. The experience of Warren and Spencer (1940) and other workers in this field has not supported this hypothesis, nor has our own experience, since the mean age of the patients studied was 45·9 years, and only three (Cases 4, 7, and

26) were hypertensive or showed any evidence of arterial degeneration. Desjardins (1932) considered that lung damage occurred more easily in thin people, and our findings accord with this view; the group of patients here recorded were significantly under-weight ($P < 0{\cdot}01$) as compared with the average weight of healthy people of the same sex, age, and height (Davenport, 1923; Kemsley, 1951–2).

The experimental irradiation of rabbits by Lüdin and Werthemann (1930) and Engelstad (1934, 1940) indicated clearly that the quantity of radiation is the most important factor, and that this is equally true for man was shown by Evans and Leucutia (1925) and Groover, Christie, Merritt, and Coe (1927). The present series shows that lung damage may occur whenever the dosage is sufficient to produce more than transient tissue-reaction. It has been seen with doses of 2,500 r. where the volume is large, as in cervico-thoracic baths, even though treatment was protracted over a month or more; while with smaller volumes and higher doses, such as 3,500 r. for routine breast fields and 5,000 r. for bronchial neoplasms, radiation damage has been much less frequently encountered. That repeated courses of deep X-ray therapy to the thorax are prone to be followed by lung damage has also been shown by Evans and Leucutia (1925), and there are many recorded cases in which severe and often fatal fibrosis has arisen in this way (McIntosh, 1934; Jacobsen, 1940; Freid and Goldberg, 1940; Warren and Spencer, 1940; Bergmann and Graham, 1951; Adams, 1951). Techniques involving the exposure of large areas of healthy lung to irradiation, such as the cervico-thoracic bath, seem particularly dangerous, and it is considered important to limit treatment as far as possible to diseased tissue. An example is Case 16, a patient with Hodgkin's disease involving the glands on the left side of the neck. Before radiotherapy the chest was normal clinically and radiologically, but because the glandular involvement appeared to spread below the left sterno-clavicular joint he was given cervico-thoracic baths. He developed the most severe radiation pneumonitis (Plate 10, Fig. 16), from which he died. Another instance was Case 18, a male civil servant with an anaplastic cellular carcinoma of the thyroid adherent to the larynx. The growth did not take up radioactive iodine, and the chest radiograph showed that it extended into the superior mediastinum, but the lung fields were clear. He was treated with cervico-thoracic baths, 3,000 r. being given anteriorly and posteriorly over a period of 30 days in 22 fractions. Ten weeks after the conclusion of radiotherapy he developed dyspnoea, and his chest radiograph showed evidence of radiation pneumonitis, which progressed and caused death less than a month later. During the last four days of life deterioration was extremely rapid, relatively mild dyspnoea progressing to death from respiratory failure within a week.

The danger of the large-single-dose technique is also emphasized. It is well recognized that this technique tends to produce severe skin reaction and adds to the dangers of lung damage. An example of this is Case 12; the patient, a 49-year-old nun, had a local mastectomy for pleomorphic carcinoma of the breast. After this operation she had deep X-ray therapy, a single dose of 1,500 r.

being given to anterior axillary, posterior axillary, internal glancing, and external glancing fields. Twelve days later she developed sickness, weakness, headache, epistaxis, high fever, and severe pain in the left shoulder, and had to be readmitted to hospital. The skin of the left chest broke down, and it was a very long time before it healed. Her left shoulder is now fixed, the skin over the left chest shows the grossest post-radiation change, and the left lung has undergone severe fibrosis (Plate 8, Fig. 9). In spite of its attractions, both to the patient and from the point of view of shortening a long waiting list for radiotherapy, the large-single-dose technique is dangerous, and should never be employed. The experimental work of Engelstad (1934 and 1940) on rabbits strongly supports this contention. He found that protraction of treatment greatly reduced the possibility of radiation damage.

It has been claimed that the simultaneous administration of anticoagulant drugs reduces the danger of pulmonary radiation damage. Boys and Harris (1943) showed that in rabbits heparinization made lung damage less likely to result from radiotherapy; Macht and Perlberg (1950) gave dicoumarol during X-ray therapy to three patients who had carcinoma of the oesophagus and to six who had lung cancer, and in spite of dosage of the order of 5,000 to 8,000 r. none of them developed any evidence of radiation fibrosis in the lungs. It is difficult to understand how anticoagulant therapy can prevent radiation damage, especially having regard to the morbid anatomical and histological appearances of lungs so affected. Cosgriff and Kligerman (1951) reported the case of a woman aged 68 years who was given radiotherapy to a secondary lung tumour; in spite of the simultaneous administration of dicoumarol, severe radiation fibrosis ensued. We are at present investigating the power of anticoagulants to protect patients against radiation damage to the lungs, but it will be a considerable time before a reliable assessment can be made. Two fatal cases have been reported in which the lung damage resulted from the occupational inhalation of radioactive dust (Belt, 1931; Tönges and Kalbfleisch, 1936); and Rajewsky (1939) reported another case in a radium-plant worker who, after three years at risk, developed dyspnoea and weakness, and died two years later. We have encountered no case in which the condition has arisen from causes other than radiotherapy, and in this country occupational hazards are so well recognized, and precautions to safeguard the worker are so excellent, that such cases are unlikely to occur. Our findings regarding the maximum breathing capacity and lung volume are similar to those reported by Leach (1943) and Baldwin, Cournand, and Richards (1949).

The differential diagnosis of radiation pneumonitis may be a matter of the greatest difficulty. Cases coming under the care of general practitioners without radiological assistance are usually diagnosed as pneumonia, and treated with antibiotics. Such a diagnostic error is not important, as the antibiotics may be of value in preventing an added infection which, in severe cases, might well turn the scale. The important problem is the differentiation between radiation pneumonitis and involvement of the lungs by growth. Even in the hands of clinicians alive to the potentialities of X-ray therapy, and even with expert

radiological help, it may be impossible to be certain whether changes in the lung are the result of irradiation or due to infiltration with growth. Many instances have been reported in which radiation damage to the lungs has been mistaken for growth and treated with further radiotherapy, with fatal results (McIntosh, 1934; Freid and Goldberg, 1940; Warren and Spencer, 1940). Case 24 illustrates

TABLE III

Points of Differentiation between Radiation Lung Damage and Lung Infiltration by Growth or Reticulosis

	Radiation pneumonitis	*Involvement of lung by growth or reticulosis*
1.	Chest radiograph showing clear lung fields before radiotherapy	
2.	Interval between radiotherapy to thorax and onset of respiratory symptoms not more than 4 months, usually much less	Interval between radiotherapy and onset of symptoms longer than 4 months
3.	Radiation skin changes present, conforming exactly to radiological area of pulmonary abnormality	Skin changes absent, or if present anatomically unrelated to pulmonary abnormality
4.	No metastases elsewhere	Metastases elsewhere
5.	Blood count normal except for moderate polymorphonuclear leucocytosis in severe cases	Often anaemia, which may be leucoerythroblastic
6.	Tendency for radiological abnormalities to diminish, and for the early development of diaphragmatic and pericardial tenting and other evidence of fibrosis	Radiological abnormalities steadily increase
7.	Symptoms: dyspnoea and dry cough	Symptoms: dyspnoea and cough. Haemoptysis may occur
8.	In non-fatal cases symptoms diminish after a few weeks	Symptoms get progressively worse.

this danger; the patient developed bilateral cervical lymphadenopathy, which gland biopsy showed to be Hodgkin's disease. Her chest X-ray showed that the paratracheal glands were involved on both sides (Plate 11, Fig. 17 *a*), and she was treated with cervico-thoracic baths (2,900 r.) over a period of five weeks. Six weeks later she noticed shortness of breath, which became progressively worse over the next fortnight; the chest X-ray then showed what was thought to be infiltration of both lung fields by lymphadenoma (Plate 11, Fig. 17 *b*). She was given 24 mg. of nitrogen mustard, and has subsequently remained free from symptoms, the chest radiograph being virtually normal (Plate 11, Fig. 17 *c*). In retrospect there seems no doubt that the lung changes were radiation pneumonitis, which fortunately the nitrogen mustard did not aggravate or prevent from regressing spontaneously. Another patient (Case 15) was given 2,750 r. by cervico-thoracic baths over a period of 29 days for cervical and intrathoracic Hodgkin's disease. A month later she developed dyspnoea, which increased rapidly, necessitating readmission to hospital. There was no cough or sputum, but she was extremely dyspnoeic and a little cyanotic, and the 'door-stop' obstruction to full inspiration was very evident to the patient and to ourselves. Her chest radiograph showed shadowing throughout both lung fields, and it was uncertain whether she was suffering from radiation pneumonitis or infiltration of her lungs by lymphadenoma. She was given first cortico-

trophin, and then triethylene melamine, but neither appeared to influence her condition, and she died from respiratory insufficiency. Although at the time it was impossible to decide the nature of her lung lesion, subsequent experience leaves little doubt that it was radiation pneumonitis. Table III shows the points regarded as most helpful in differentiation between radiation pneumonitis and lung involvement by growth. Cases of lung damage limited to one apex, after breast irradiation, have to be differentiated from pulmonary tuberculosis. The history of radiotherapy and the absence of tubercle bacilli in the sputum should be a sufficient guide; but a patient who had radiation damage to the lung after mastectomy was given a prolonged course of streptomycin in consequence of this diagnostic error.

The morbid anatomical and histological features of pulmonary radiation damage have been well described by a number of writers. Engelstad (1934) and Lüdin and Werthemann (1930) described the appearances in rabbits, Warren and Gates (1940) in rats, dogs, and pigs, as well as rabbits, and Tullis (1949) has supplied a full report of the findings in swine which died as a result of the atom-bomb explosion at Bikini in 1946, and in others used as experimental animals. Such descriptions accord closely with the many publications concerning human lungs damaged by radiation (Hines, 1922; Evans and Leucutia, 1925; Groover, Christie, Merritt, and Coe, 1927; McIntosh, 1934; McIntosh and Spitz, 1939; Schairer and Krombach, 1939; Rajewsky, 1939; Jacobsen, 1940; Freid and Goldberg, 1940; Warren and Spencer, 1940; Liebow, Warren, and DeCoursey, 1949; Bergmann and Graham, 1951; Hutchison, 1953). The findings in our three patients who came to autopsy were exactly similar to those described by the above-mentioned writers. There is no single histological finding which is diagnostic of radiation damage. For example, the hyaline membrane may be evident in anyone who has been dyspnoeic during the last hours of life, whatever the cause of death (Farber and Wilson, 1932 *a*, *b*), while the increase of elastic tissue is also seen in healed infarcts and apical scars. It is the combination of many or all of the various abnormalities which is so strongly suggestive of radiation as a cause, but, even so, all these abnormalities are sometimes found in patients who have not been exposed to X-rays (Warren and Spencer, 1940). The aetiology of such cases is often not clear, but Hutchison (1953) has pointed out that oil pneumonias can produce very similar appearances.

It is remarkable how rarely bronchiectasis complicates radiation fibrosis of the lungs. Only one of our patients (Case 1) had any substantial quantity of sputum. This apparent immunity to superimposed infection is considered to be due largely to the fact that the upper zones of the lungs are those principally affected by radiation. The dry irritating cough and the dyspnoea on exertion are sometimes relieved a little by ephedrine and a codeine linctus, but apart from simple measures such as these the mild cases are better left without treatment. In the severe cases antibiotics should be given during the pneumonitis stage, and corticoid therapy for four to six weeks. Avoidance, as far as possible, of radiotherapeutic techniques favouring the development of lung damage is obviously of the first importance, as is also the recognition of such

damage when it does develop. Fortunately it is uncommon, and usually resolves spontaneously, albeit incompletely.

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APPENDIX

I. *Case Reports*

Case 1. A woman aged 48 years, who three years previously had had a right radical mastectomy for carcinoma, followed by routine radiotherapy. Thereafter she had a cough, dyspnoea on exertion, and, after an attack of pneumonia the following year, copious purulent sputum. Examination showed slight dyspnoea at rest, radiation changes in the skin over the right chest, a slightly œdematous right arm, and the physical signs of fibrosis of the right lung. Sputum was copious and purulent. Chest radiographs showed fibrosis of the right lung, and a bronchogram showed crowded right bronchi. The vital capacity was 1·2 litres, and the maximum breathing capacity 29·5 litres per minute. Bronchoscopy and air sampling from both lungs showed the right lung to be without function. Hysterical aphonia followed this procedure. The blood showed a gross iron-deficiency anaemia (red cells 3,550,000 per c.mm., haemoglobin 56 per cent., mean corpuscular haemoglobin concentration 28·3 per cent., mean corpuscular volume 76·6 c.μ), and a fractional test meal showed achlorhydria. Treatment with iron, penicillin, and breathing exercises produced so much improvement that it was decided not to proceed with right pneumonectomy, especially in view of the patient's psychological instability.

Case 2. A woman aged 39 years had a right radical mastectomy for spheroidal-celled carcinoma with heavy infiltration of the axillary lymph-nodes. After operation radiotherapy was given (tumour dose 3,000 r.) to routine breast fields in 20 fractions over 26 days. Thereafter she had dyspnoea on exertion, and a tendency to chest colds. Four months after the conclusion of X-ray treatment she developed a cough, and pain in the right shoulder and chest. The chest radiograph showed fibrosis in the right upper zone, and fractured ribs on the right side. Gross radiation changes in the skin were evident over the right chest, especially in front; the right upper limb was oedematous, movement of the right shoulder was limited, and X-rays showed osteoporotic changes in the right shoulder and humerus. No special investigations or treatment were undertaken.

Case 3. A woman aged 63 years, a life-long neurotic, had had a right radical mastectomy for anaplastic polyhedral-celled carcinoma with extensive involvement of the axillary lymph-nodes. After operation a tumour dose of 3,500 r. was given to routine breast fields in 18 fractions over 27 days. Thereafter she had dyspnoea on exertion, and 10 months later a cough and pain in the right axilla. There were radiation changes in the skin over the right upper thorax, and clinical signs of fibrosis of the right upper lobe. The chest expansion was one inch. No evidence was found of recurrence of the growth. The chest radiograph showed fibrosis of the right upper lobe. No further investigation was undertaken, and no treatment given.

Case 4. A woman aged 57 years had had a left radical mastectomy for carcinoma in 1952, followed by radiotherapy over 24 days, a tumour dose of 3,000 r.

being given to routine fields in 10 fractions. Three months later cough and dyspnoea occasioned a chest radiograph, which showed shadowing in the left upper and right lower zones. Metastases were presumed, and testosterone therapy instituted. The X-ray appearances cleared remarkably, but cough, with scanty sputum and dyspnoea, persisted, and tightness on swallowing and regurgitation of unaltered food developed. Pneumonia in 1954 led to further investigation. The chest radiograph showed displacement of the mediastinum to the left and shadowing in the right lower zone. A barium-swallow examination showed two localized oesophageal indentations, but no gastric reflux. A barium meal showed a complete disruption of the gastric mucosal pattern, but a normal gastric outline and mobility. Oesophagoscopy showed mucosal changes and mild oozing of blood all down the oesophagus, the cardia at 38 cm., and 2 cm. of gastric mucosa in the chest; the gastric mucosa appeared normal. She also had benign essential hypertension.

Case 5. A woman aged 48 years had a left radical mastectomy for polyhedral-celled carcinoma with involvement of the axillary glands. A 3,500-r. tumour dose was given through routine breast fields in 21 fractions over 30 days. The chest radiograph before operation was normal. One month after the conclusion of radiotherapy she developed dyspnoea and a dry cough, which increased for three months and then receded. Examination revealed no evidence of recurrence, but radiation changes in the skin over the left chest in front and behind; the chest expansion was two inches, and there were clinical and radiological signs of fibrosis of the left apex. No further investigations or treatment were undertaken.

Case 6. A woman aged 44 years had had a right radical mastectomy for carcinoma, followed by radiotherapy (tumour dose 3,500 r.) to routine breast fields. She never had any respiratory symptoms, and there were no abnormal physical signs, but a chest radiograph six months later showed mild radiation changes in the right upper lobe. The patient also has disseminated sclerosis.

Case 7. A woman aged 64 years, diabetic, and with a blood-pressure of 180/90. The pedal pulses were absent. Left radical mastectomy was performed for carcinoma, followed by deep X-ray therapy (tumour dose 3,500 r.) to routine breast fields. Thereafter she had dyspnoea on exertion. A year later a chest radiograph revealed slight radiation fibrosis in the left upper lobe. No further investigation or treatment was undertaken.

Case 8. A woman aged 43 years had a left radical mastectomy for scirrhous carcinoma with axillary lymph-node involvement. The chest radiograph was normal before operation. Afterwards radiotherapy (3,450 r. tumour dose) was given through routine breast fields in 17 fractions over 24 days. One month later she developed dyspnoea, cough, and soreness behind the sternum. The cough and dyspnoea have persisted. The chest expansion was one and a half to two inches. Radiation changes were present in the skin over the left upper chest, and there were clinical and radiological signs of fibrosis in the left upper lobe (Plate 6, Fig. 5). No further investigations were undertaken, and only symptomatic treatment was given.

Case 9. A woman aged 62 years had had radical amputation of the right breast when 50 years old, followed by radiotherapy. Seven years later a routine chest radiograph showed fibrosis of the right upper lobe. She had no symptoms at any time.

Case 10. A woman aged 49 years had a 13-years' history of goitre, which had been increasing in size for five years and was associated with symptoms and signs of thyrotoxicosis. The basal metabolic rate was +61 per cent. The chest

radiograph showed retrosternal extension and multiple pulmonary metastases. Partial thyroidectomy was done, and histological examination showed adenocarcinoma. The secondary growths in the chest did not take up radioactive iodine, and repeated doses, totalling 198 mc., did not prevent them increasing in size, and caused myxoedema. Radiotherapy was given by anterior and posterior thoracic baths, an incident dose of 2,900 r. being given in 21 fractions over 29 days. Thereafter she developed dyspnoea, cough, and radiological evidence of radiation damage to the lungs, and death followed from respiratory insufficiency.

Case 11. A man aged 54 years had had a bronchitic tendency since two attacks of pneumonia in the First World War. When 50 years old he had a left total and right partial thyroidectomy, with block dissection of the glands of the neck, for undifferentiated carcinoma of the thyroid. The glands extended retrosternally into the mediastinum. The chest radiograph was clear apart from calcified pleura and an old injury to the left fifth rib. He was given radiotherapy by cervico-thoracic baths—an incident dose of 3,000 r. in four weeks. Afterwards 'pneumonia' was treated by his own doctor. He has since shown diminution in exercise tolerance, with the chest expansion one and three-quarter inches, and radiological evidence of bilateral pulmonary fibrosis.

Case 12. A woman aged 49 years had local removal of the left breast for pleomorphic carcinoma, followed by deep X-ray therapy, a single dose of 1,500 r. being given to anterior axillary, posterior axillary, internal glancing, and external glancing fields. Twelve days later she had pyrexia, epistaxis, vomiting, and pain in the left shoulder. The skin of the left chest was raw. The ultimate result was virtually complete destruction of the left lung by fibrotic changes (Plate 8, Fig. 9), a fixed left shoulder, and gross radiation changes in the skin over the left chest. She has had no respiratory disability.

Case 13. A man aged 45 years had an anaplastic carcinoma of the left lower-lobe bronchus, producing collapse of the left lower lobe, paradoxical movement of the left diaphragm, and displacement of the oesophagus to the right. He was treated with deep X-rays, a central axis dose of 2,630 r. being given in 14 days through parallel opposing anterior and posterior 15×15 cm. fields in 14 days. Three weeks later the chest radiograph was virtually normal, and all symptoms had disappeared. Two months after this he had some cough, and dyspnoea on exertion, and the chest radiograph showed shadowing at both apices, especially the left, which appeared to be due to radiation fibrosis and not to residual or recurrent growth. He also developed transient auricular fibrillation, for which no cause was apparent. Recurrence of growth later became evident, and the patient is now dying.

Case 14. A woman aged 42 years had a right radical mastectomy for an intraduct and infiltrative carcinoma with secondary invasion of lymphnodes. After operation radiotherapy was given through routine breast fields (tumour dose 2,700 r., given in 18 fractions over 23 days). Later skin nodules appeared in the treated area and, local treatment failing, were finally controlled by further irradiation, following the routine technique, but giving a minimum tumour dose of 5,000 r. in 10 fractions over 10 weeks, to the chest wall only. One month after the last X-ray treatment slight cough developed. A chest radiograph showed fibrosis of the whole of the right lung, with displacement of the mediastinum to the right and tenting of the right diaphragm. The chest expansion was one and a half inches. Two months later a severe respiratory infection appeared to greatly aggravate all these abnormalities.

Case 15. A woman aged 38 years had Hodgkin's disease involving glands in the right supraclavicular fossa, right axilla, and superior mediastinum. She had irregular pyrexia and anaemia (red cells 3,220,000 per c.mm., haemoglobin

43 per cent.). She was treated by blood transfusion, iron, and cervico-thoracic baths, an incident dose of 2,750 r. being given in 21 treatments over 29 days. One month after the conclusion of radiotherapy she developed dyspnoea on exertion, and felt an obstruction in the chest preventing full inspiration. Two weeks later she was readmitted to hospital, dyspnoeic and cyanotic at rest, but with a normal blood count and no lymphadenopathy. Examination showed a marked 'door-stop' catch on attempts at full inspiration, chest expansion two inches, maximum breathing capacity 36·6 litres per minute, and vital capacity 2·05 litres. The chest radiograph showed shadowing spreading out from both hila into the lung fields (Plate 6, Fig. 6). She was treated with corticotrophin (20 mg. daily by slow intravenous drip) for 10 days, without improvement. Diaphragmatic and pericardial tenting developed, as shown on chest radiographs. The diagnosis was regarded as uncertain, and oral triethylene melamine was given without benefit. The patient died from respiratory insufficiency, with no further evidence of Hodgkin's disease. There was no autopsy.

Case 16. A man aged 21 years had Hodgkin's disease involving the glands on the left side of the neck. There was no other objective abnormality; the chest radiograph was clear, and the blood count normal. He was given cervico-thoracic baths (2,450 r. incident dose in 20 treatments over 28 days). Seven weeks later he developed an increasing dry cough, and dyspnoea on exertion. The chest expansion was $\frac{7}{8}$ inch, and there was a marked 'door-stop' obstruction to full inspiration. A chest radiograph showed fan-shaped shadowing throughout both lung fields, and tenting of the diaphragm and pericardium on the left side (Plate 10, Fig. 16). The maximum breathing capacity was 63·5 litres per minute, vital capacity 1·26 litres, and residual volume/total capacity ratio 42 per cent. The arterial oxygen saturation at rest was 92·9 per cent., and on exercise 83·3 per cent.; the arterial carbon-dioxide content at rest 46·35 per cent., and on exercise 44·55 per cent. He was given 1·5 gm. of cortisone intramuscularly over 13 days, after which there was considerable subjective improvement; the chest expansion was two and a quarter inches, maximum breathing capacity 110 litres per minute, vital capacity 1·47 litres, residual volume/total capacity ratio 40 per cent., and arterial oxygen saturation at rest 92·3 per cent. and on exercise 87·5 per cent. No further evidence of Hodgkin's disease developed, and he died at home six months later from respiratory insufficiency. No autopsy was obtained.

Case 17. A man aged 30 years had Hodgkin's disease involving glands on both sides of the neck. The chest radiograph showed enlargement of hilar and paratracheal glands on the right side, but clear lung fields. He was given cervico-thoracic baths (3,000 r. incident dose over 26 days). One month later dyspnoea and a dry cough developed. These symptoms increased, and he was readmitted to hospital four weeks later. He was then dyspnoeic and cyanotic at rest, with the chest expansion two inches, and 'door-stop' obstruction to full inspiration. The chest radiograph showed shadowing radiating out from both hila; the maximum breathing capacity was 39 litres per minute, and vital capacity 0·79 litre. He was treated with oxygen, cortisone, and corticotrophin, but deteriorated rapidly, and died 72 hours after admission. Autopsy showed bilateral pleural effusions and firm, rubbery, airless lungs, with the pleurae thickened and showing irregular depressed scars. Histological examination showed striking loss of alveolar space due to thickening and fibrosis of alveolar walls, swelling of alveolar lining cells, and the presence within alveoli of hyaline membrane, organizing exudate, foamy macrophages, and desquamated cells. Fibrosis was evident especially around the vessels and bronchi, and there was much thickening and fragmentation of the elastica. There was no evidence of Hodgkin's disease in the lungs (Plate 8, Figs. 10, 11).

Case 18. A man aged 56 years had a mass in the right lobe of the thyroid, adherent to the larynx and producing obstruction of the thoracic inlet. The chest radiograph was clear, apart from extension of the mass into the superior mediastinum. Laryngoscopy showed invasion of the larynx. Biopsy showed an anaplastic cellular carcinoma of the thyroid. The gland did not take up radio-iodine. Radiotherapy was given by cervico-thoracic baths, an incident dose of 3,000 r. being administered in 22 fractions over 30 days. Ten weeks later there was complete regression of the primary growth, and no sign of metastatic growth, but dyspnoea developed, and the chest radiograph showed radiation changes in the lungs. Death took place from respiratory insufficiency three weeks after the onset of dyspnoea, and before the patient could be admitted to hospital. No autopsy was obtained.

Case 19. A man aged 79 years was treated with supervoltage radiotherapy at another centre for histologically proven carcinoma of the oesophagus. At the conclusion of treatment he was forced to retire to bed because of dyspnoea. Four weeks later radiography showed gross bilateral radiation pneumonitis, with restriction of diaphragmatic movement. A barium-swallow examination showed no mass within the oesophagus, but the cardia two inches above the diaphragm, and free reflux of gastric contents. Death took place a week later. Autopsy showed the lungs to be firm and fibrotic, with pleural adhesions on the left and an effusion on the right side. Histologically there were numerous thin-walled abscesses, and bronchopneumonic consolidation at the bases, as well as the usual changes seen in radiation damage to the lungs.

Case 20. A woman aged 60 years. When 57 years old she had a left radical mastectomy for polygonal-celled carcinoma. Three years later right radical mastectomy was done for polygonal-celled scirrhous carcinoma with secondary deposits in the regional glands. After the second operation radiotherapy was given to routine breast fields (tumour dose 3,000 r. in 13 fractions over 18 days). The chest radiograph before radiotherapy was normal. Two or three months after the conclusion of X-ray treatment dyspnoea on exertion, and tightness of the chest on taking a deep breath, became evident. The chest expansion was one and a half inches. The chest radiograph showed tenting of the right diaphragm and shadowing in the right upper zone (Plate 6, Fig. 7). The maximum breathing capacity was 34 litres per minute, vital capacity 2·56 litres, and residual volume/total capacity ratio 24 per cent. She was treated with oral cortisone, 100 mg. daily, for 30 days, at the conclusion of which symptoms had disappeared, chest expansion was three inches, and the chest radiograph still showed right upper-zone fibrosis, but the shadowing was less marked; the maximum breathing capacity was 64 litres, and the vital capacity 2·59 litres.

Case 21. A woman aged 44 years had had a right radical mastectomy for intra-duct and intra-acinar carcinoma, followed by radiotherapy, a tumour dose of 3,000 r. being given to routine breast fields in 20 fractions over 28 days. A year later a metastasis in the first cervical vertebra was treated with testosterone and further radiotherapy, a dose of 1,250 r. being given in a single treatment to right, left, and posterior cervical fields. A year later glands appeared in the left supraclavicular fossa, and there was evidence of obstruction to the superior vena cava, which appeared on chest radiography to be due to secondary growth at the left hilum spreading to the left apex. Deep X-ray therapy was given to the left supraclavicular area, and a dose of 3,000 r. was given anteriorly and posteriorly to the mediastinum. Thereafter the patient was troubled by cough, and was short of breath on exertion. A chest radiograph showed fibrosis of both upper zones, especially the left, and fractured sixth and seventh right ribs. There has been no evidence of further metastases for three years.

Case 22. A woman aged 26 years had painless lymphadenopathy in the right supraclavicular fossa. Biopsy showed Hodgkin's disease. The chest radiograph showed gross involvement of the mediastinal glands, but clear lung fields. She was given deep X-ray therapy, 2,750 r. to anterior and posterior mediastinal fields and 3,000 r. to the right supraclavicular fossa, in 10 fractions over 12 days. Four months later, after a cold, she developed cough and severe dyspnoea on exertion, which improved with aureomycin, but thereafter her exercise tolerance was always restricted. A year later the chest expansion was one and a half inches; the chest radiograph showed fibrosis in both upper zones, corresponding to area of minimal residual changes in the skin. Screening showed tenting of the central portions of the diaphragm on inspiration, but the lateral portions moved well. A barium-swallow examination showed a normal oesophagus. The maximum breathing capacity was 24 litres per minute, total lung volume 3·33 litres, vital capacity 1·90 litres, residual volume 1·43 litres, and residual volume/total capacity ratio 43 per cent. There was no evidence of recurrence of lymphadenoma.

Case 23. A woman aged 69 years had a left local mastectomy for poorly differentiated carcinoma. The chest radiograph was normal before operation. After operation radiotherapy was given to routine breast fields (tumour dose 3,500 r. in 20 fractions over 28 days). Two weeks later she developed a troublesome, irritable cough, and after another three weeks was treated by her own doctor for 'pneumonia'. When seen 10 weeks after the conclusion of radiotherapy she had a persistent cough, and the chest radiograph showed fibrosis of the left upper lobe.

Case 24. A woman aged 21 years had bilateral painless lymphadenopathy in the supraclavicular fossae. Biopsy showed sclerosing Hodgkin's disease. The chest radiograph showed bilateral enlargement of the paratracheal glands, but clear lung fields (Plate 11, Fig. 17 *a*). Deep X-ray therapy was given by cervicothoracic baths (2,900 r. incident dose in 27 fractions over five weeks). Six weeks after the conclusion of radiotherapy, increasing dyspnoea developed. The chest radiograph showed shadowing throughout both lung fields (Plate 11, Fig. 17 *b*), which was regarded erroneously as infiltration by lymphadenoma, and she was given 24 mg. of nitrogen mustard. During the subsequent three years there have been no symptoms, and no evidence of recurrence of Hodgkin's disease. The chest radiograph is now virtually normal (Plate 11, Fig. 17 *c*), and the chest expansion three inches.

Case 25. A woman aged 36 years had a right radical mastectomy for scirrhous carcinoma with early involvement of the axillary lymph-nodes, followed by deep X-ray therapy to routine breast fields (tumour dose 3,450 r. in 15 fractions over 18 days). Three months later she developed dyspnoea. The chest radiograph showed the mediastinum displaced to the right, tenting of the right diaphragm, and shadowing throughout the right lung field.

Case 26. A woman aged 62 years had advanced carcinoma of the left breast, treated wholly by radiotherapy (6,850 r. tumour dose in 10 weeks through left internal and external glancing fields). Three months later she had a tumour in the right breast, and was given a 4,800 r. tumour dose through right internal and external glancing fields over six weeks. Two months later she developed glands in the right axilla, and a further dose of 3,000 r. was given to right anterior and posterior axillary fields, in 10 fractions over two weeks. The chest radiograph 10 weeks later showed the mediastinum displaced to the right, shadowing throughout the right lung, especially the upper lobe, and some shadowing in the left lower zone. The patient also has benign essential hypertension.

Case 27. A woman aged 27 years. Nine years previously she had had local radiotherapy for histologically proven Hodgkin's disease involving the glands on the right side of the neck, and four years later further local radiotherapy for glands in the left supraclavicular fossa. She was well for five years; then further glands appeared in the right supraclavicular fossa, and the chest radiograph showed glands in the right side of the mediastinum. Local radiotherapy was given to the right supraclavicular fossa, and 3,000 r. to anterior and posterior mediastinal fields in 10 treatments over 13 days. Four weeks later dyspnoea on exertion and dry cough developed. The chest radiograph showed lung shadowing corresponding exactly to the area of radiation change in the skin (Plate 7 Fig. 8). The chest expansion was one and a quarter inches, the maximum breathing capacity 47 litres per minute, vital capacity 2·05 litres, and residual volume/total capacity ratio 35 per cent. She was given 505 mg. of corticotrophin by slow intravenous drip in 17 days, after which there was marked subjective improvement, the chest expansion was two and three quarter inches, maximum breathing capacity 119 litres per minute, and vital capacity 2·63 litres. There was no further evidence of Hodgkin's disease, and no change in the respiratory state, during a three-year follow-up.

Case 28. A man aged 18 years had lymphosarcoma involving the glands on the left side of the neck. No other abnormality was found; the chest radiograph was clear, and the blood count normal. He was given cervico-thoracic baths (2,900 r. incident dose in 22 treatments over 32 days). Three weeks later he developed a dry, irritating cough, and increasing dyspnoea on exertion. A fortnight later he was dyspnoeic and cyanotic at rest; the chest expansion was one and a quarter inches, with marked 'door-stop' obstruction to full inspiration; the chest radiograph showed fan-shaped mottling spreading throughout both lung fields, with tenting of the left diaphragm (Plate 10, Fig. 14). The maximum breathing capacity was 71·4 litres per minute, vital capacity 1·30 litres, and residual volume/total capacity ratio 62 per cent. He was given 890 mg. of corticotrophin by slow intravenous drip in 35 days, and after this was dyspnoeic only on severe exertion. A chest radiograph showed considerable clearing of the lung fields, and further evidence of fibrosis (Plate 10, Fig. 15); the chest expansion was three and a half inches, and the maximum breathing capacity became 185 litres per minute, the vital capacity 2·88 litres, and residual volume/total capacity ratio 28 per cent. There was no recurrence of lymphosarcoma, and no change in the respiratory state, during a three-year follow-up.

Case 29. A woman aged 46 years had a left local mastectomy for massive medullary carcinomatous involvement of the breast and axillary tissue. Before operation the chest radiograph was normal. After operation a tumour dose of 3,500 r. was given through routine breast fields in 20 fractions over 35 days. Two weeks later she had a 'chest cold', which lasted one month. Four months later she developed secondary deposits in the pelvis and femur, which were treated with testosterone and further radiotherapy. Seven months after the conclusion of X-ray treatment to the thorax she developed dyspnoea and cough. The chest radiograph showed displacement of the mediastinum to the left, and fibrosis of the left upper lobe; the remaining lung fields, however, were not normal. The maximum breathing capacity was 65 litres per minute, total lung capacity 2·56 litres, vital capacity 1·63 litres, and residual volume/total capacity ratio 36 per cent. Dyspnoea and cough increased, cyanosis developed, and death occurred about 10 weeks after the development of respiratory symptoms. Autopsy showed secondary carcinoma and radiation changes in all lobes of both lungs (Plate 9, Figs. 12, 13). Secondary carcinoma was also present in the vertebrae, pelvis, skull, and liver.

II. *Radiotherapeutic Technique*

In the preceding case protocols the term 'routine irradiation' in the cases of breast cancer refers to the usual technique employed in the Radiotherapy Department of the United Birmingham Hospitals. In this procedure the axilla and supraclavicular region are treated by two opposed 25×10 cm. fields. The anterior field is placed with the medial lower angle over the inner end of the contralateral first rib space, and the centre line of the applicator crosses the tip of the coracoid process of the scapula. The field is directed in the coronal plane, and is strictly opposed by the posterior field, at a separation of about 16 cm. in most cases. The chest wall is treated by two parallel opposed fields, 15×10 cm., separated by 16 cm., applied tangentially to the chest wall immediately below the axillary-supraclavicular fields, the inner margin lying on the parasternal line in the first rib space. The treatment factors in each field are: 50 cm. F.S.D., 230 kv., and H.V.L. 2·0 mm.Cu. All fields are treated daily. The tumour dose is defined as the minimum dose on the central axis. The cervico-thoracic bath involves irradiation of the neck, supraclavicular regions, both axillae, lung fields, and mediastinum, in a radiation field of 30×30 cm. at 100 cm. F.S.D., 230 kv., and H.V.L. 0·5 mm. Cu. The total dose delivered is governed by the fall in the white-cell count, the daily dose being 150 r. and the maximum incident dose 3,000 r. The dose in the mediastinum is between 70 per cent. and 100 per cent. of the incident dose. The dose in the lung fields cannot be estimated accurately.

Summary

Twenty-nine cases are reported in which radiation damage to the lungs followed radiotherapy applied to the thorax. The aetiological, diagnostic, and therapeutic aspects are discussed.

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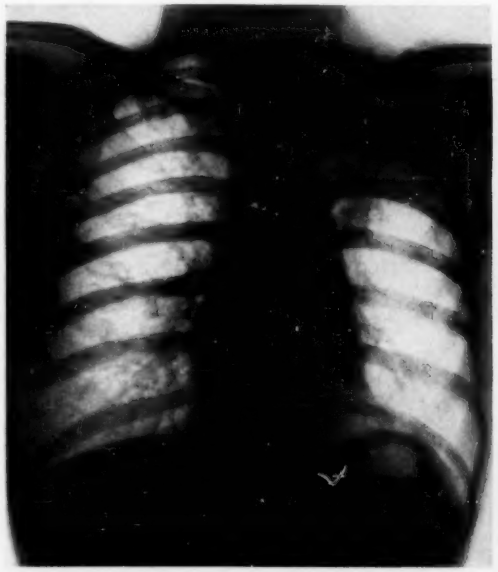

FIG. 5. Case 8. Pneumonitis stage of damage to the lungs from radiation after mastectomy

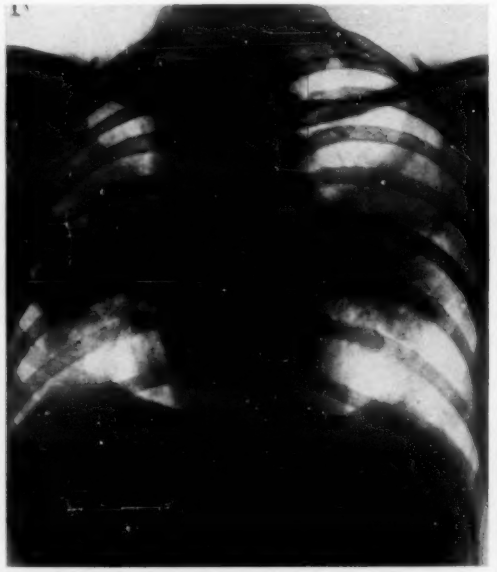

FIG. 6. Case 15. Pneumonitis stage of radiation damage to the lungs after cervico-thoracic baths for Hodgkin's disease

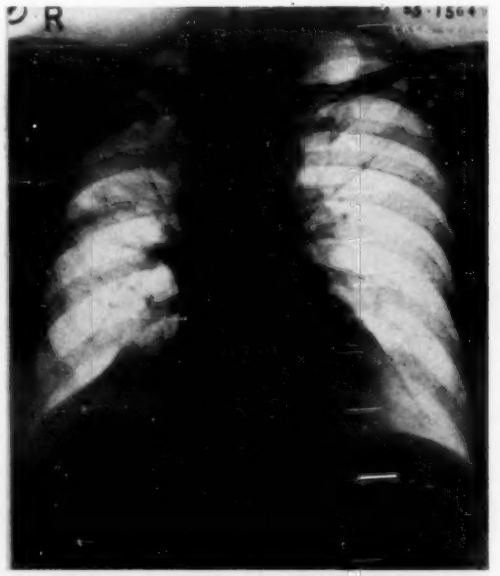

FIG. 7. Case 20. Pleural and pericardial tenting and mediastinal shift, due to radiation fibrosis from radiotherapy after mastectomy

FIG. 8 (*a*), (*b*), and (*c*). Case 27. Relationship between the area of skin change due to radiation and the extent of radiation damage to the lungs. X-ray treatment had been given through anterior and posterior mediastinal fields for involvement of the mediastinal glands by lymphadenoma

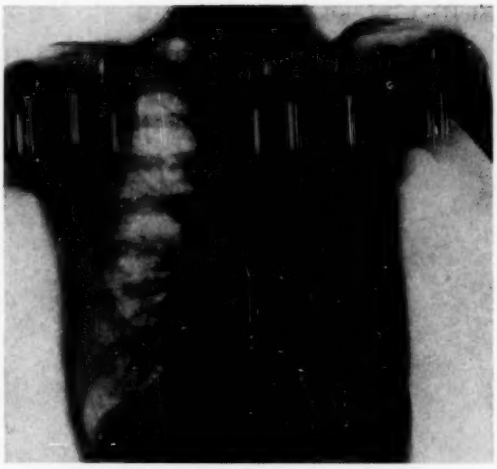

FIG. 9. Case 12. Almost complete destruction of the left lung by radiotherapy after mastectomy (large single dose technique)

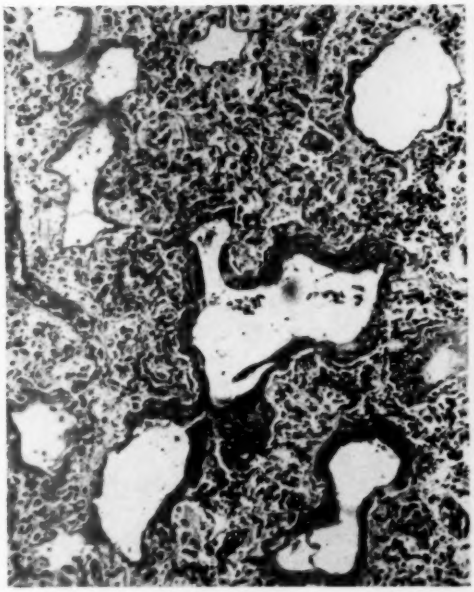

FIG. 10. Case 17. Dilated alveolar ducts and alveoli lined by hyaline membrane. Many alveoli are collapsed, and others contain large numbers of macrophages (haematoxylin and eosin, × 80)

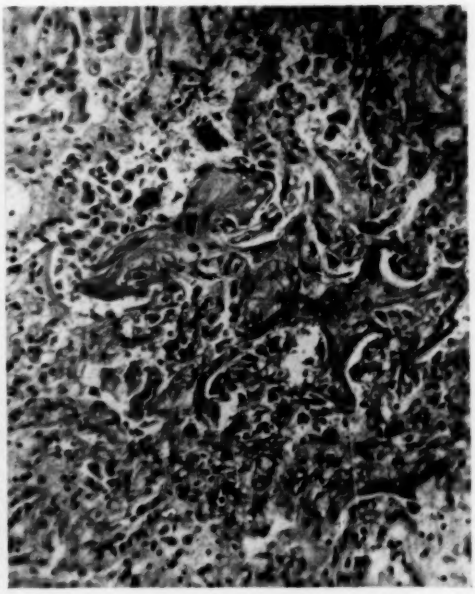

FIG. 11. Case 17. The alveolar walls are thickened and fibrotic, and organized exudate is present within the lumen. Numerous macrophages and large distorted cells are seen in the alveoli, and some of the latter appear to be desquamated from alveolar walls (haematoxylin and eosin, × 150)

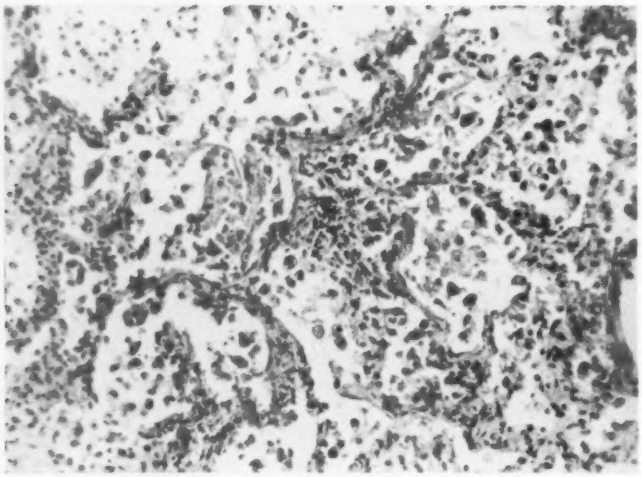

FIG. 12. Case 29. The alveolar walls are hyalinized and infiltrated with lymphocytes. Large numbers of macrophages, many of which contain lipoid, are present within the lumen (haematoxylin and eosin, ×120)

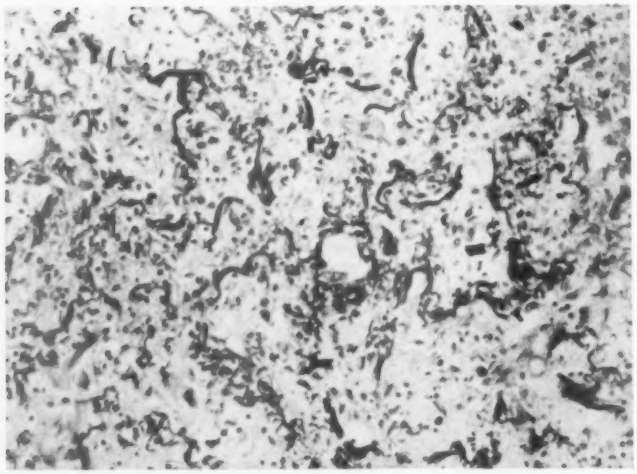

FIG. 13. Case 29. Thickening and fragmentation of elastica (Lawson's modification of the Weigert-Sheridan elastic stain, × 160)

FIG. 14. Case 28. Severe pneumonitis before corticoid therapy

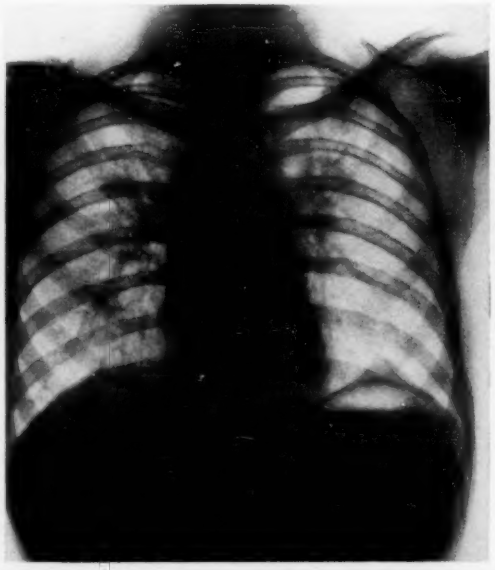

FIG. 15. Case 28. Improvement after three and a half weeks' corticoid therapy

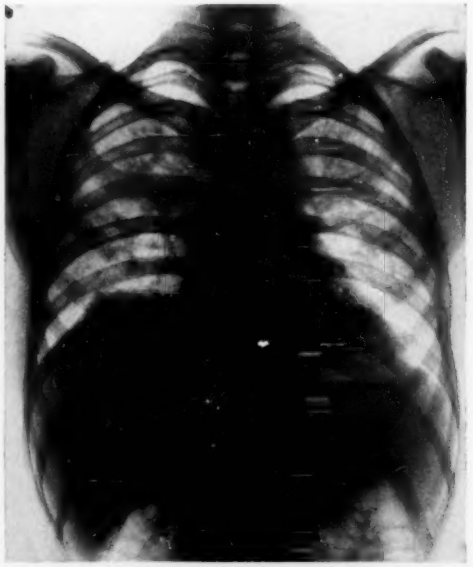

FIG. 16. Case 16. Fatal radiation damage to the lungs after cervico-thoracic baths for Hodgkin's disease involving the cervical glands

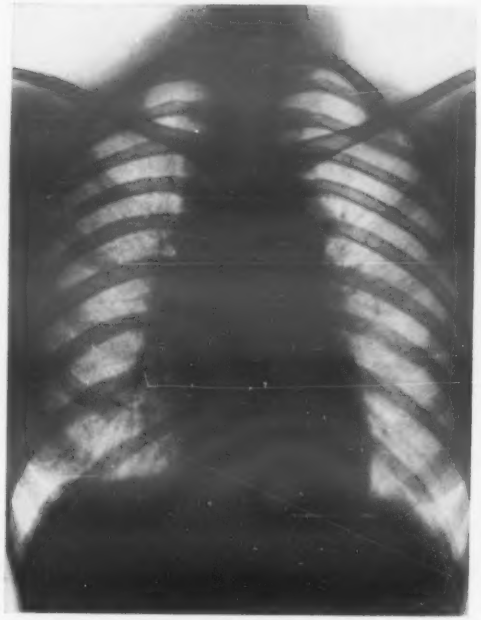

FIG. 17 *a*. Case 24. Before radiotherapy. Bilateral involvement of paratracheal glands by Hodgkin's disease, and clear lung fields

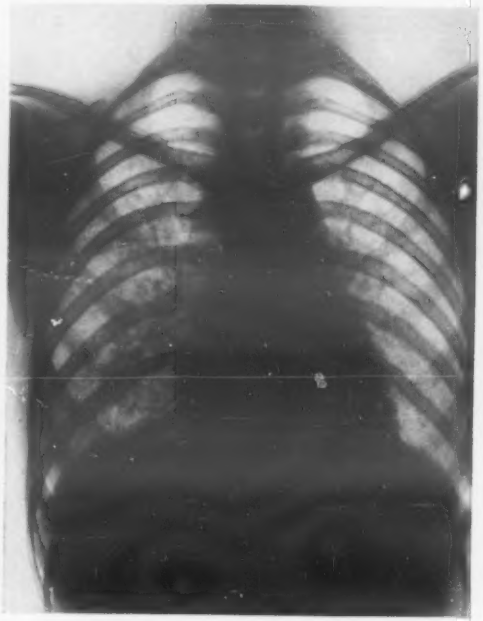

FIG. 17 *b*. Case 24. Mild radiation pneumonitis after cervico-thoracic baths

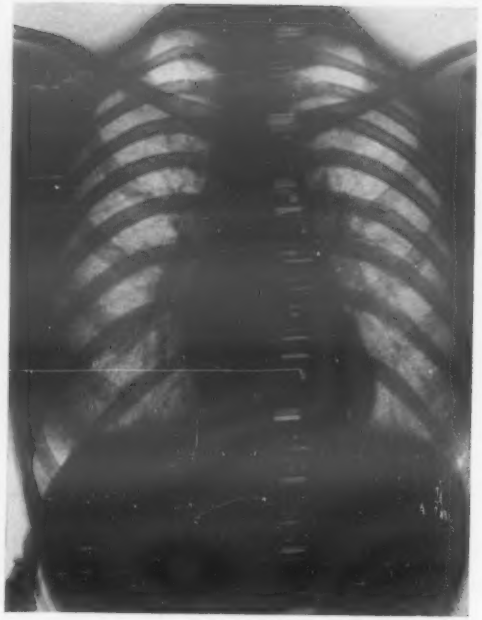

FIG. 17 *c*. Case 24. Regression of radiation pneumonitis and disappearance of enlarged glands

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THE MEGALOBLASTIC ANAEMIAS[1]

Their Investigation and Classification

By RONALD H. GIRDWOOD

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In recent years new methods have been developed to assist in the study of the megaloblastic anaemias. This has greatly improved our competency to explain the mechanism of production of the various types of megaloblastic anaemia, and to diagnose difficult clinical problems. The methods that have become available for such studies include:

1. Biopsy of the gastric mucosa by means of a narrow flexible tube containing a suitable cutting instrument (Wood, Doig, Motteram, and Hughes, 1949). The value of this method is limited, because atrophic gastritis may be present not only in pernicious anaemia but also in iron-deficiency anaemia.

2. Estimation of the serum vitamin-B_{12} level, using *Euglena gracilis* (Hutner, Provasoli, Stokstad, Hoffmann, Belt, Franklin, and Jukes, 1949; Mollin and Ross, 1952) or *Lactobacillus leichmannii* (Rosenthal and Sarett, 1952; Girdwood, 1954*a*) as test organism.

3. A differential test of urinary folic-acid excretion, in which the patient is given 5 mg. of pteroylglutamic acid[2] by injection, and then 5 mg. of the same substance by mouth. After each of these doses the urinary output of folic acid is measured, and a significantly low output after the oral dose indicates malabsorption of folic acid (Girdwood, 1953*a*).

4. Measurement of intrinsic-factor activity and of vitamin-B_{12} absorption. This may be done by giving by mouth cyanocobalamin labelled with radioactive cobalt, either to a patient under investigation, or, together with a gastric juice under investigation, to a patient known to have pernicious anaemia (Heinle, Welch, Scharf, Meacham, and Prusoff, 1952; Callender, Turnbull, and Wakisaka, 1954). Absorption occurs normally only if intrinsic factor is present, and may be estimated by measurement of radioactivity in the stools, or in the urine after a 'flushing' injected dose of cyanocobalamin (Schilling, 1953), or by direct measurement over the liver with a scintillation counter (Glass, Boyd, and Gellin, 1955).

[1] Received July 25, 1955.

[2] Although there are several natural substances with folic-acid activity, the name folic acid is commonly taken in clinical practice to be synonymous with pteroylglutamic acid; hence such a simplification will be used in this paper where therapy is discussed. Where this test is being considered, however, it is perhaps preferable to use the name pteroylglutamic acid for the substance being administered, but folic acid for the product excreted in the urine.

The present account is based upon the study of over a thousand cases of megaloblastic anaemia in India and Burma during the Second World War, and in Great Britain and the United States thereafter. In recent years the patients have been investigated particularly by means of the *L. leichmannii* assay of the serum vitamin-B_{12} level and by the differential test of urinary folic-acid excretion. The haematological terminology used is essentially that of Israëls (1941).

Methods

The principle of microbiological assay is that an organism which requires a certain substance for its growth is allowed to grow in a suitable medium, to which are added various dilutions of that essential substance. The amount of growth is measured turbidimetrically or by other means, and a standard curve is drawn. The material (for example, serum or urine) being tested for the presence of this growth factor is added in suitable dilution to the medium, and this mixture, too, is inoculated with the test organism. The amount of growth will depend upon the quantity of the growth factor present, and the result can be calculated directly from the standard curve. The serum vitamin-B_{12} level was estimated by a modification of the method of Rosenthal and Sarett (1952), as already described (Girdwood, 1954*a*), with *L. leichmannii* as test organism. The modification consisted of halving the amount of sodium acetate in the medium, and replacing the fumaric and ascorbic acids by thioglycolic acid; 160 mg. of the latter was added to 400 ml. of double-strength medium. The cyanocobalamin standard and the diluted sera were autoclaved with the medium. The amount of growth was estimated turbidimetrically, rather than from the quantity of acid produced. With this method it has been possible to obtain 90 to 120 per cent. recovery of 200 $\mu\mu$g. of added cyanocobalamin per 1 ml. of serum. Differential tests of urinary folic-acid excretion were made by the method already described (Girdwood, 1953*a*). The urinary output of folic acid was estimated in the 24-hour specimens of urine collected respectively after subcutaneous and oral test doses of 5 mg. of pteroylglutamic acid. As will be seen later, the output after the oral test dose of 5 mg. normally exceeds 1·6 mg., and, under the conditions of the test (in some instances with the prior administration of injections of folic acid for a few days to correct 'desaturation'), an output of less than 1·6 mg. after the oral dose indicates malabsorption. The results may be expressed as follows:

$$\frac{\text{24-hour urinary output of folic acid after 5 mg. of pteroylglutamic acid by mouth}}{\text{24-hour urinary output of folic acid after 5 mg. of pteroylglutamic acid subcutaneously}} \times 100.$$

For convenience this ratio, expressed as a percentage, is given the letter R. Normally R = 75 to 150 per cent. The test organism was *Streptococcus faecalis*. From the point of view of the hospital ward staff the collection of specimens for these tests is an easy matter; indeed some tests were done on a domiciliary basis. Few routine hospital laboratories would wish to embark upon micro-

biological assay methods, but in cases of difficult diagnosis specimens can be posted to a suitable laboratory. We are at present investigating the possibility of measuring the folic-acid output by fluorometry. It is reasonable to suggest that the demonstration, by the test here described, of malabsorption of synthetic pteroylglutamic acid, is an indication that the patient cannot absorb in a normal manner the naturally occurring folic-acid substances of the diet. On the other hand it cannot be assumed that the demonstration of normal absorption of the synthetic substance is necessarily an indication that a patient can absorb in a normal manner the naturally occurring folic-acid complexes.

The Nutritional Megaloblastic Anaemias

Modern methods of investigation have not yet been much used in the investigation of the nutritional megaloblastic anaemias, and the author's personal experience is limited to the years 1943 to 1946, when thousands of cases occurred in Indian troops east of the Brahmaputra river in the fighting areas of Assam and Burma (Girdwood, 1948; Passmore, 1949). It will be recalled that, in a series of papers commencing in 1931, Wills and her colleagues described megaloblastic anaemia occurring in male and female subjects in the Bombay area. The anaemia responded to autolysed yeast preparations given by mouth, and to injections of 'crude' liver extract (campolon), but not to injections of 'refined' liver extract (anahaemin). Many believe that the active substance was folic acid. Unfortunately it is not now possible to obtain samples of the batches of the therapeutic agents used at that time in order to carry out the necessary assays, and the amount of folic acid present in modern liver extracts is very small. In addition, not only do we not know the minimum amount of folic-acid substances required to produce a haemopoietic response in human beings with primary folic-acid deficiency, but we must also accept the fact that the only way to measure dietetic deficiency of substances such as folic acid and vitamin B_{12} is to carry out investigations while the subjects lead their normal lives at home, and to analyse the food as cooked by them. The method and length of time of cooking has a pronounced effect on the folic-acid content of foodstuffs. Even when such investigations are done, it cannot be said with certainty that substances with folic-acid or vitamin-B_{12} activity for micro-organisms have haemopoietic activity for man. It is probable that nutritional macrocytic anaemia varies in its causation not only from country to country, but also in different areas of the same country. To a certain extent the picture has been confused by various authors stressing only one of the factors in the area in which they are working, without giving due attention to others. It seems likely that in the Bombay area the patients were suffering primarily from folic-acid deficiency, aggravated in many instances by pregnancy. In Calcutta, too, Das Gupta, Chatterjea, and Basu (1953) have recently shown the importance of folic-acid deficiency, but the patients seen by Fairley, Bromfield, Foy, and Kondi (1938) among Macedonian refugees could hardly have been suffering from folic-acid deficiency when their diet consisted so largely of fresh

fruit and vegetables. There vitamin-B_{12} deficiency may have predominated, and malaria was very common. It is difficult to understand why nutritional macrocytic anaemia is reported as not uncommonly megaloblastic in Kenya (Foy and Kondi, 1954), but normoblastic in Uganda (Trowell, 1947; Lehmann, 1949). Woodruff (1955), working in Nigeria, has stressed the importance of protein malnutrition and liver damage as a cause of nutritional macrocytic anaemia with a macronormoblastic marrow. In the present paper, however, our concern is with the nutritional megaloblastic anaemias, rather than with the whole range of nutritional macrocytic anaemias.

To illustrate the difficulties involved in analysing the causation of nutritional megaloblastic anaemia in the tropics, brief reference may be made to the condition as it occurred in Indian troops on the eastern fighting front in the Second World War. There megaloblastic anaemia was very commonly seen. One unexplained fact is that the condition was geographical in occurrence. It was reported only from areas east of the Brahmaputra river, and although the present author saw hundreds of cases east of the river, he did not see a single case west of it except in men being evacuated or going on leave from the fighting areas. None of the patients seen in the course of the investigation died while under observation, but deaths were reported from other hospitals despite all attempts at treatment. Macrocytic anaemia was almost unknown in the extensive investigations carried out by Hynes (1945) amongst Indian army troops and new recruits in central and western India. Factors that may have been of importance were:

1. Malnutrition before joining the Army, possibly giving poor tissue-stores of folic acid and vitamin B_{12}. In jungle fighting, too, there were temporary difficulties in supplying rations.

2. Unaccustomed severe exertion in the jungle.

3. Infection in the fighting areas with a strain of malaria different to that to which the men had previously been exposed. This caused red-cell destruction in men whose bodily stores of antimegaloblastic substances may already have been depleted. Thus malaria might cause normoblastic anaemia in British troops, but megaloblastic anaemia in Indian soldiers.

4. The occurrence of sprue in the fighting areas. British troops were affected by sprue in these regions, and many Indians had watery or bulky stools. Gilroy (1949) has pointed out that steatorrhoea cannot occur unless there is sufficient fat in the diet, and it is of interest that French (1955) has suggested that the megaloblastic anaemia in these Indians was due, not to malnutrition, but to sprue occurring where there was an increase in the fat ration and substitution of vegetable oils and fats for butter fats. The problem of the geographical incidence of nutritional megaloblastic anaemia would on this basis be similar to that of the geographical incidence of sprue.

5. Changes in intestinal flora cannot be excluded as a factor. This, however, is a problem for which no satisfactory method of investigation has yet been devised.

6. Helminthic infestation. About a third of the men investigated by us for

nutritional megaloblastic anaemia showed evidence of infestation with ankylostome. Lehmann (1949) has suggested that macrocytic anaemia in Uganda is largely due to reticulocytes and young cells appearing in the peripheral blood in response to bleeding from ankylostomiasis, but Hynes (1945) did not find macrocytic anaemia in Indian troops, even when ankylostome infestation was heavy. On the other hand, where other factors are tending to cause megaloblastic anaemia, continued bleeding from parasitic infestation may well increase

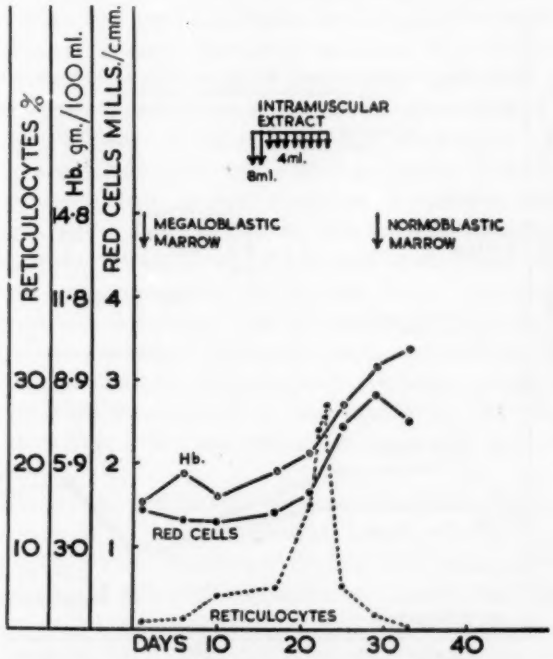

FIG. 1. Megaloblastic anaemia in an Indian soldier. Response to liver injections.

the need for haemopoietic factors that are not available to the host. Many of our patients had macrocytosis without showing an increase in the proportion of reticulocytes.

Two illustrative examples may be given from the patients seen at that time.

Case 1. An Indian soldier, aged 18 years, with one and a half years' service. He had served in Chittagong for four months, having previously been in central India. Unlike most of those seen during the investigation, he had taken no part in jungle warfare. He stated that the food he had received was satisfactory, but little credence could be given to such statements by these patients. He was a vegetarian. There had been no diarrhoea, and no glossitis. Three weeks previously he had had malignant tertian malaria, which was treated with mepacrine. The haemoglobin level was 4·6 gm. per 100 ml., red cells 1,435,000 per c.mm., and reticulocytes 1·5 per cent., and the marrow was frankly megaloblastic. As is shown in Fig. 1, there was a satisfactory response to injections of

a batch of liver extract which had been clinically tested in pernicious anaemia and found satisfactory. Unfortunately none of the extract is now available for estimation of its cyanocobalamin content. It was not marketed as a 'crude' extract, but further reference to the use of this term is made below.

Case 2. An Indian soldier, aged 28 years, who had spent five months of his two years of service on the Arakan front. He had the general symptoms of anaemia, and occasional loose motions. Seven months previously he had had

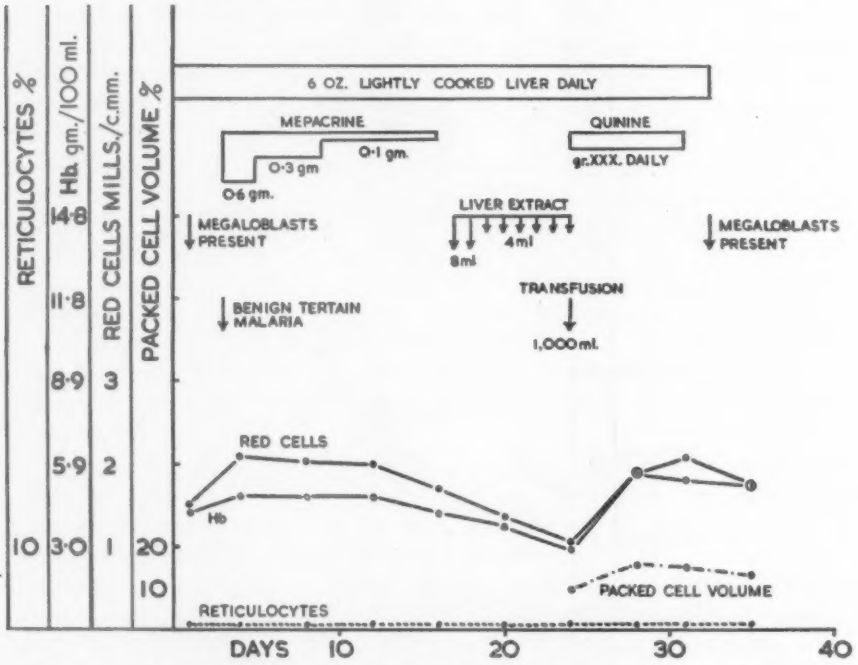

FIG. 2. Megaloblastic anaemia in an Indian soldier. No response to liver injections or liver by mouth.

malaria, and after that had been treated he had taken suppressive mepacrine regularly. The patient, who was a meat eater, claimed that his food had been satisfactory. The spleen was palpable and tender, and the tongue was normal. The patient had already been treated with mepacrine, iron, autolysed yeast (½ oz. twice daily for two weeks), and 6 oz. of lightly cooked fresh liver daily by mouth for a week. The haemoglobin level was 4·2 gm. per 100 ml., red cells 1,535,000 per c.mm., and reticulocytes less than 1 per cent. The marrow was very cellular, and contained megaloblasts. Suppressive mepacrine was stopped, and parasites of benign tertian malaria appeared in the blood four days later. As will be seen from Fig. 2, there was no response to injections of the same batch of liver extract as had been given to Case 1, to antimalarial therapy, or to a further 32 days' treatment with lightly cooked liver by mouth. Thereafter the patient was evacuated to a Base Hospital, and it was not possible to follow his further progress.

Our experience of measuring the content of vitamin B_{12} and folic-acid substances in liver extracts manufactured during and just after the war years (Girdwood and Carmichael, 1950) makes us unwilling to suggest that there was any consistent difference between 'crude' and 'refined' liver extracts manufactured at that time. On the whole 'crude' liver extracts contained less vitamin B_{12} than did 'refined' ones, but this was not always the case, and there was great variation from batch to batch. The content of folic-acid substances has exceeded 1 μg. per ml. in only two out of 35 batches of liver extract that we have tested. One of these was a pre-war 'crude' extract, and the other was a post-war 'refined' extract. It may, however, be said that these two cases illustrate the difference in response to the same therapeutic agent that is commonly found in cases of megaloblastic anaemia in the tropics. The first patient may have been suffering primarily from vitamin-B_{12} deficiency aggravated by malarial infection and, unlike most of the cases seen in the course of the investigations, he responded rapidly to liver injections. The second did not respond to this treatment, and it may be that he was mainly deficient in folic acid. However, whether the deficiency was of folic acid or of vitamin B_{12} or of both, it is necessary to infer either some complicating factor, such as malaria, that prevented any response occurring to the administration of lightly cooked liver, a source of both these antimegaloblastic substances, or intestinal malabsorption, preventing a response to any of the therapeutic agents given by mouth. Few of the patients responded satisfactorily to liver injections. The majority slowly recovered or, as in Case 2, did not respond to treatment. A number died at Base Hospitals.

No doubt further light will be thrown upon the aetiology of the nutritional megaloblastic anaemias by modern methods of investigation, such as estimation of vitamin B_{12} in the serum. Unfortunately, as will be explained subsequently, a low urinary output of folic acid may follow an injected test dose of pteroylglutamic acid when the primary deficiency is of vitamin B_{12}, and on the other hand a normal output may follow the injected dose of pteroylglutamic acid when the patient is depleted of folic acid. Accordingly, although, as can be seen later, our results suggest that the differential test of urinary folic-acid excretion can be used to measure folic-acid absorption, they do not suggest that the first part of the test is of value in differentiating between megaloblastic anaemia due to dietary deficiency of folic acid and that due to dietary deficiency of vitamin B_{12}. The value of measurements of the folic acid in the blood has not yet been established. In the light of present knowledge it appears reasonable to suggest that the nutritional megaloblastic anaemias comprise the following types:

Those due to deficiency of folic-acid substances.

Those due to deficiency of vitamin B_{12}.

Those due to deficiency of both (probably this includes most cases).

Those due to deficiency of either or both, with other conditions, such as pregnancy, sprue, malaria, or changes in intestinal flora aggravating the deficiency.

Macronormoblastic anaemia of protein deficiency and resultant liver disease, with superadded megaloblastic anaemia from deficiency of antimegaloblastic substances.

Pernicious Anaemia (Addisonian Pernicious Anaemia)

The term pernicious anaemia is unscientific and incorrect in that the condition is no longer pernicious; but the name is so firmly established that it should perhaps be retained for the present, provided it is applied solely to the type of megaloblastic anaemia resulting from intrinsic-factor deficiency due to genetic defect or perhaps, as gastric biopsy suggests, sometimes to atrophic gastritis. Usually pernicious anaemia may be readily diagnosed clinically, but from time to time a case may occur in which there is some difficulty in establishing the diagnosis. This is particularly so when there appear to be subacute combined degeneration of the cord and histamine-fast achlorhydria without megaloblastic anaemia. Fortunately a diagnosis may now be established in such cases before treatment by measurement of the vitamin B_{12} in the serum.

Case 3. A 52-year-old seaman was referred to the Edinburgh Dental Hospital in May 1954 because of a painful mouth, and was provided with new dentures, which caused some improvement. From there he was referred to the Blood Clinic, where no abnormality was found on physical examination, there being no neurological features. The tongue was red and smooth, but examination of the blood showed haemoglobin 12·4 gm. per 100 ml., red cells 3,740,000 per c.mm., colour index 1·1, packed cell volume 36 per cent., mean corpuscular volume 96·2 c.μ, reticulocytes less than 1 per cent., and white cells 7,400 per c.mm. The film appeared normal. The marrow was normoblastic, and there was histamine-fast achlorhydria. The serum vitamin-B_{12} level, however, was less than 50 $\mu\mu$g. per ml. (normal 130 to 750 $\mu\mu$g. per ml.). The patient returned to sea without treatment, and in August 1954 he had no symptoms and the blood levels were haemoglobin 14·1 gm. per 100 ml., red cells 3,570,000 per c.mm., colour index 1·3, and vitamin B_{12} less than 50 $\mu\mu$g. per ml. Later in that month he noticed that his hands were becoming stiff and numb, with a feeling of 'pins and needles'. The feet were similarly affected, and he noticed that he staggered when he walked. There was no dyspnoea, and no loss of weight. On examination in October 1954 the patient looked healthy. The tongue was clean and smooth, and the papillae were atrophied. There was absence of vibration sense in the lower limbs, and the grip was impaired. Romberg's sign was present. The plantar responses were flexor. The haemoglobin level was 14·4 gm. per 100 ml., red cells 3,680,000 per c.mm., packed cell volume 41 per cent., mean corpuscular volume 111·4 c.μ., and mean corpuscular haemoglobin concentration 35 per cent. The marrow did not contain frank megaloblasts, but a few transitional erythroblasts (sometimes named transitional megaloblasts) were found with difficulty. There was histamine-fast achlorhydria. The serum vitamin-B_{12} level was still less than 50 $\mu\mu$g. per ml. Cyanocobalamin was given by injection, and there was a satisfactory clinical and haematological response, the haemoglobin level rising to 15·4 gm. per 100 ml. and the red-cell count to 5,130,000 per c.mm.

Comment. This case was one of pernicious anaemia, in which neurological complications occurred when the marrow contained some transitional erythro-

blasts but no frank megaloblasts. An abnormal serum vitamin-B_{12} level was found when the only symptom was a painful mouth, and the marrow was still normoblastic.

Mollin and Ross (1953), using the *Euglena* assay of the serum vitamin-B_{12} concentration, found that, when single injections of cyanocobalamin were given to patients with untreated pernicious anaemia, early megaloblastic

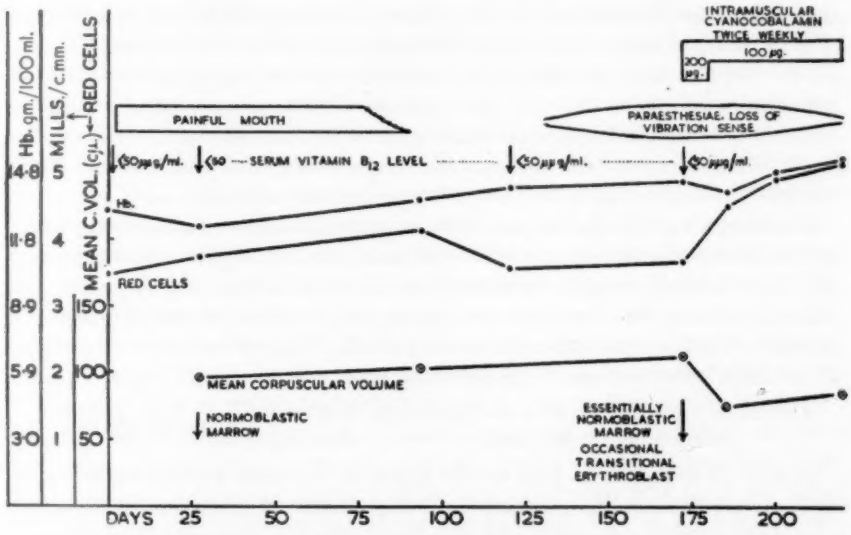

FIG. 3. Serum vitamin-B_{12} deficiency preceding megaloblastic anaemia.

change reappeared a few days after the serum vitamin-B_{12} concentration fell again below 100 $\mu\mu$g. per ml. Our findings in the above case, and in some of the patients who had gastrectomy, indicate that, where megaloblastic anaemia is about to develop, the fall in the serum vitamin-B_{12} level may precede megaloblastic changes in the marrow. We have no direct knowledge of the relationship between the bodily stores of vitamin B_{12} and the level of this substance in the serum, and do not know to what extent bodily stores of folic-acid substances may play a part in maintaining normoblastic blood formation when the serum vitamin-B_{12} level is falling. It should also be realized that a low serum vitamin-B_{12} level may be found in association with a normoblastic marrow in patients who have pernicious anaemia, and have been treated with substances other than cyanocobalamin that have antimegaloblastic activity. The most obvious of these substances is folic acid, which is contained in many of the 'blunderbuss' haematinics which, unfortunately, are sometimes prescribed. Folic acid is included, too, in at least one of the multiple-vitamin preparations that are advertised and on direct sale to the public in Britain. Severe iron-deficiency may occasionally cause a diagnosis of pernicious anaemia to be overlooked, as in a 47-year-old patient who had a haemoglobin level of 6·5 gm. per 100 ml. and

a red-cell count of 3,590,000 per c.mm. (colour index 0·6, packed cell volume 24 per cent., mean corpuscular volume 66·8 c.μ, mean corpuscular haemoglobin concentration 27·1 per cent.). There was no response to iron therapy, and so the marrow was examined and found to be megaloblastic. In such a case estimation of the serum vitamin-B_{12} level will help in establishing that the case is one of pernicious anaemia. Of 75 cases of untreated pernicious anaemia the serum vitamin-B_{12} level, estimated by the *L. leichmannii* method, has been below 50 $\mu\mu$g. per ml. in 49 instances. In the others, with the exception of two patients seen at an early stage of the investigations, the level has been below 130 $\mu\mu$g. per ml. In 120 patients without any cause for vitamin-B_{12} deficiency the level has been from 130 to 750 $\mu\mu$g. per ml. (mean 299·9 $\mu\mu$g. per ml.). Pernicious anaemia is sometimes a familial disease, but three non-anaemic members of a family whose parents *both* had pernicious anaemia were found to have serum vitamin-B_{12} levels of 245, 290, and 360 $\mu\mu$g./ml. respectively.

It should be noted that in pernicious anaemia the differential test of urinary folic-acid excretion shows no evidence of malabsorption of pteroylglutamic acid and that, although there is frequently a diminished output of folic acid in the urine after an injected test dose of pteroylglutamic acid in untreated pernicious anaemia, this diminution is not invariably found. When it does occur the results of the differential test are of the following type:

Output after 5 mg. given subcutaneously: 0·25 mg.
after 5 mg. given orally: 2·10 mg. } R = 840 per cent.

It may be argued here that bodily stores of folic-acid substances are used up in metabolic reactions normally involving vitamin B_{12}, and that the injected dose of pteroylglutamic acid is utilized in correcting the 'folic-acid desaturation'. Reference, however, is made later to the value or inadequacy of such a test as an index of folic-acid depletion. Where a patient suspected of having pernicious anaemia is referred for diagnosis after commencement of therapy, absorption studies using labelled vitamin B_{12} may be of value. It is suggested that vitamin-B_{12} deficiency caused primarily by a failure of the production of intrinsic factor may occur:

1. With a megaloblastic anaemia;
2. Without a megaloblastic anaemia, as discussed above. This is rare; or
3. Complicated by other causes of megaloblastic anaemia (for example, pregnancy, tropical sprue, gastric carcinoma).

Megaloblastic Anaemia due to Idiopathic Steatorrhoea and Related Diseases

The term 'sprue syndrome' or 'malabsorption syndrome' is applied to a series of conditions which may show marked variation as regards clinical features, and may differ in their causation. The patient may have glossitis, bulky diarrhoea, and megaloblastic anaemia, or simply an iron-deficiency anaemia failing to respond to iron preparations given by mouth. Such clinical features may be produced, not only by tropical sprue and idiopathic steator-

rhoea, but also by coeliac disease, regional jejunitis, tumours, strictures, ulcers, fistulae, and reticuloses of the small intestine, and by tuberculosis, tumours, or reticuloses of the mesenteric glands. In many centres on the American continent it is considered that sprue is due primarily to dietary deficiency, but this view is not held in Britain or generally in the East.

In the patient with glossitis, bulky diarrhoea, and megaloblastic anaemia, the diagnosis is usually obvious without complicated tests, especially if there is free hydrochloric acid in the gastric contents. Where biochemical tests are necessary, the methods of investigation commonly employed are the fat-balance test, the glucose-absorption test, and examination of the X-ray pattern of the small intestine (Cooke, Peeney, and Hawkins, 1953). We have found the folic-acid absorption test to be more consistently and definitely positive in such cases than the fat-balance test as undertaken in routine laboratories, and hospital ward staffs have found it much easier to carry out. It must be admitted however that, unlike measurement of faecal fat, the microbiological assay of the specimens is not a procedure that can be carried out as an occasional test in a routine laboratory. Table I shows the results of the folic-acid absorption test in the 30 adult patients investigated who have had intestinal malabsorption of the type under consideration. It will be seen that in all but two instances the urinary output of folic acid, after the oral dose of 5 mg., was less than 1·6 mg. Differential tests of urinary folic-acid excretion were carried out in 70 control patients without megaloblastic anaemia, malignancy, or clinical features suggesting a malabsorptive disease, and the urinary output of folic acid after the 5 mg. oral dose ranged from 1·63 to 4·58 mg. (mean 2·76 mg.). In these control cases the output after the 5 mg. *injected* dose of pteroylglutamic acid ranged from 1·85 to 4·83 mg. (mean 3·08 mg.). Previous folic-acid therapy had not been given. It should, however, be noted that many of the patients shown in Table I had been treated with folic acid for months or years before the differential urinary excretion test was carried out. It is reasonable to consider that the tissues and organs of these patients were not depleted of the substance. It should be further realized that the marrow findings recorded for patients who had had this form of therapy were the findings before the folic-acid treatment was given. In contrast, the blood counts given in the Table are those done at the time of the differential test of urinary folic-acid excretion.

It will be seen from Table I that two patients (Cases 16 and 18) had megaloblastic marrows together with normal serum vitamin-B_{12} levels, and yet showed a normal output of folic acid after the injected dose. The same was true of another patient (Case 27), whose marrow contained intermediate erythroblasts rather than frank megaloblasts. These patients responded to folic-acid therapy. This suggests that, although a low output of folic acid after the injected test dose may indicate folic-acid deficiency, the reverse is not true. *A normal output does not indicate that the patient is not desaturated.* No doubt the factors involved include the degree of desaturation and the relationship between the rate of excretion of folic acid by the kidneys and of its uptake by depleted tissues; the matter merits further investigation.

TABLE I

Results of Differential Urinary Folic-Acid Excretion Test in Cases of Intestinal Malabsorption of the Sprue Type

Case number	Sex	Age (years)	Diagnosis	Folic-acid therapy given before test	Marrow before folic-acid therapy	Blood counts at time of absorption test: Haemoglobin (gm./100 ml.)	Blood counts at time of absorption test: red cells (millions/c.mm.)	Urinary folic-acid excretion (mg.): (a) After 5 mg. subcutaneous	Urinary folic-acid excretion (mg.): (b) After 5 mg. oral	R $\left(\frac{b}{a} \times 100\right)$	Fat-balance test in routine laboratory (% absorbed)	Serum vitamin-B_{12} ($\mu\mu$g./ml.)
4	F	33	Adult coeliac	Yes	*Megaloblastic	10·2	4·32	4·18	0·009	0·22	87	..
5	F	39	'Refractory megaloblastic anaemia'	Yes	*Megaloblastic	14·6	4·92	3·21	0·021	0·65	93 (prev.)†	260
6	M	33	Idiopathic steatorrhoea	No	Megaloblastic	5·5	2·11	1·46	0·030	2·1	..	270
7	M	42	Tropical sprue	Yes	..	16·1	5·65	3·02	0·036	1·2	53	..
8	M	42	Idiopathic steatorrhoea	Yes	*Megaloblastic	13·3	5·34	4·90	0·048	0·98	84 (prev.)	160
9	F	72	Idiopathic steatorrhoea	No	Megaloblastic	5·6	3·28	0·677	0·051	7·5	68	..
10	M	49	Idiopathic steatorrhoea	Yes	*Megaloblastic	9·7	3·84	1·29	0·055	4·3	57 (prev.)	..
11	F	36	Idiopathic steatorrhoea	Yes	*Megaloblastic	7·4	2·80	2·40	0·080	3·3	..	..
12	F	16	Adolescent coeliac	No	..	14·6	5·0	2·30	0·082	3·6	..	440
13	M	23	Idiopathic steatorrhoea	Yes	*Megaloblastic	12·9	3·34	1·80	0·089	4·9	96	..
14	F	36	'Refractory megaloblastic anaemia'	Yes	*Megaloblastic	11·5	3·10	4·60	0·16	3·5	..	..
15	F	55	Tabes mesenterica	Yes	..	10·0	4·19	2·42	0·18	7·4	81 (prev.)	..
16	F	60	Idiopathic steatorrhoea	No	Megaloblastic	12·4	4·17	3·00	0·196	6·5	96	520‡
17	M	36	Tropical sprue	Yes	*Megaloblastic	14·0	4·39	3·41	0·20	5·9	81 (prev.)	..
18	F	47	Regional jejunitis	No	Megaloblastic	10·1	3·71	2·69	0·21	7·8	66	180
19	F	44	Refractory iron-deficiency anaemia	No	Normoblastic	8·7	4·54	0·87	0·21	24·1	96	230
20	F	38	Idiopathic steatorrhoea	No	Megaloblastic	5·0	1·49	2·80	0·26	9·3	..	..
21	M	45	Idiopathic steatorrhoea	Yes	*Megaloblastic	13·2	5·24	4·38	0·27	6·2	84	..
22	M	52	Idiopathic steatorrhoea	No	Normoblastic	15·2	5·02	2·52	0·33	13·1	80	120
23	F	42	Idiopathic steatorrhoea	Yes	*Megaloblastic	12·7	5·80	1·95	0·38	20·0	84 (prev.)	370
24	M	35	Idiopathic steatorrhoea	No	Megaloblastic	6·2	2·17	1·35	0·42	31·1	..	250
25	F	54	'Refractory megaloblastic anaemia'	Yes	*Megaloblastic	13·2	4·62	1·97	0·53	26·9	97·4	300
26	F	17	Adult coeliac	No	Normoblastic	7·4	5·32	2·51	0·61	24·3	86	..
27	M	28	Idiopathic steatorrhoea	No	Intermediate erythroblasts	7·0	3·07	3·12	0·79	25·3	..	160
28	M	21	Adult coeliac	No	Normoblastic	12·5	3·67	2·39	0·79	33·1	..	160
29	F	45	Idiopathic steatorrhoea	No	Normoblastic	7·5	4·53	3·90	0·85	21·8	80	270
30	M	22	Idiopathic steatorrhoea	Yes	Normoblastic	11·4	4·84	4·10	1·20	29·3	78 (prev.)	280
31	F	48	'Refractory megaloblastic anaemia'	Yes	*Megaloblastic	14·5	4·86	4·95	1·30	26·3	..	310
32	F	26	Idiopathic steatorrhoea	Yes	Normoblastic	13·2	4·61	3·27	1·61	49·2	85 (prev.)	..
33	M	41	Idiopathic steatorrhoea	Yes	*Megaloblastic	11·9	4·15	4·59	2·07	45·1	..	140
		43	(same patient)	Yes		13·8	4·59	1·50	0·43	28·7	85	150

* Note that these marrows were examined before any folic-acid treatment was given, and not just before the folic-acid excretion test. In some instances this treatment had been given for months or years after the marrow puncture had been done.

† (Prev.) indicates that the fat-balance test had been done on a previous occasion, and not at the time of the folic-acid excretion test.

‡ Cyanocobalamin injections had been given.

In general, the patients in Table I with the poorest absorption of folic acid from the alimentary tract were more ill than those with less abnormal absorption. Two of the patients shown in this Table had an output exceeding 1·60 mg. after the oral dose. One (Case 32) was a patient who had had no symptoms or signs for five years, and who had been maintained on folic-acid therapy. Case 33 is referred to below. It is of interest to compare the results of the differential test of urinary folic-acid excretion with those of the fat-balance test. It will be seen from Table I that four patients (Cases 13, 16, 19, and 25) had normal results from the fat-balance test, but a poor excretion of folic acid after the oral test dose of pteroylglutamic acid. The diet for the fat-balance test was supplied from a dietetic ward, and the stools were collected over two four-day periods: the stools were analysed for fat-content in a routine laboratory. All these patients had other evidence of malabsorption. One of them (Case 13) had a flat glucose-absorption curve, an X-ray pattern of intestinal malabsorption, and intermittent tetany. Case 16 is considered below. In Case 19 there was iron-deficiency anaemia, which responded only to iron preparations given by injection; it was possible to demonstrate a flat iron-absorption curve in this patient. The fourth patient (Case 25) had intermittent bulky diarrhoea and malabsorption of glucose, iron, and ascorbic acid. There is no reason for supposing that the demonstration of malabsorption of pteroylglutamic acid in these patients is an incorrect observation, and in at least three of the four cases the clinical evidence suggested that malabsorption of fat was also a feature. This merely indicates that misleading results may be obtained from fat-balance tests of short duration carried out under routine hospital conditions. It will be seen that in only one of the cases investigated (Case 22) was the serum vitamin-B_{12} level less than 130 $\mu\mu$g. per ml., the figure that we have taken as the lower limit of normal.

The following examples are given to illustrate the practical value of the differential test of urinary folic-acid excretion.

Case 5. A woman aged 39 years was found in May 1951 to have iron-deficiency anaemia that failed to respond to iron therapy by mouth. The blood levels were: haemoglobin 8 gm. per 100 ml.; red cells 4,060,000 per c.mm.; mean corpuscular volume 71·4 c.μ; mean corpuscular haemoglobin concentration 27·6 per cent. A test meal showed free hydrochloric acid in the gastric juice, and the marrow was normoblastic. There was a good response to treatment with saccharated iron oxide given intravenously, the haemoglobin level rising to 14·6 gm. per 100 ml. There was no obvious source of blood loss, the diet was satisfactory, and there was no diarrhoea. The patient felt so well with the parenteral iron therapy that she ceased attending as an out-patient. In October 1953 she was admitted to a hospital in another town, with a haemoglobin level of 8·2 gm. per 100 ml. and a red-cell count of 2,680,000 per c.mm. The marrow was megaloblastic, and a fat-balance test showed 92·6 per cent. absorption of fat. The serum vitamin-B_{12} level was 260 $\mu\mu$g. per ml. (*Euglena* assay). The patient was considered to be suffering from idiopathic refractory megaloblastic anaemia, and was treated with vitamin B_{12} and folic acid simultaneously. There was a very good response. In November 1953 the physician

who had been treating the patient kindly permitted us to do a differential test of urinary folic-acid excretion, and the result was:

Output after 5 mg. given subcutaneously: 3·21 mg.
after 5 mg. given orally: 0·021 mg. } R = 0·65 per cent.

Comment. This was a case of 'refractory iron deficiency' followed by 'refractory megaloblastic anaemia', without diarrhoea, and with a normal fat-balance test, due, in fact, to intestinal malabsorption particularly of iron and folic acid.

Case 16. A woman aged 60 years was seen at an out-patient clinic because of loss of weight, bulky diarrhoea, and anaemia. Her diet was normal. Apparently, because the haemoglobin level was 9·8 gm. per 100 ml. and the red-cell count 2,300,000 per c.mm. (colour index 1·47), the patient was diagnosed as having pernicious anaemia and treated with liver injections, a 'refined' preparation being used. There was a satisfactory response, but subsequently a slight relapse, the red-cell count never, however, falling below 4,000,000 per c.mm. For three months before her admission to hospital cyanocobalamin was given instead of liver injections, in a dosage of 100 μg. fortnightly, and at the time of admission the haemoglobin was 12·4 gm. per 100 ml., and red cells 4,170,000 per c.mm. The serum vitamin-B_{12} level was 520 $\mu\mu$g. per ml. The marrow showed a megaloblastic tendency. There was a high level of free hydrochloric acid in the gastric juice. The stools appeared bulky, but a routine fat-balance test over two four-day periods gave normal results (94·8 per cent. and 96·3 per cent. absorption). A barium follow-through examination with ordinary barium showed no abnormality. Meantime, however, a differential test of urinary folic-acid excretion had shown malabsorption of folic acid, the result being:

Output after 5 mg. given subcutaneously: 3·0 mg.
after 5 mg. given orally: 0·196 mg. } R = 6·5 per cent.

The patient showed a response to folic-acid therapy.

Comment. It is of interest that this patient at first showed a response to liver injections. The other features were that a 'routine' fat-balance test gave only misleading results, and that, although there is every reason to believe that the patient was suffering from desaturation of folic-acid substances, this could not be demonstrated by measuring the urinary output after an injected test dose of 5 mg. of pteroylglutamic acid. There was, however, considerable malabsorption of folic acid.

Case 22. A man aged 52 years had two spontaneous fractures in the pelvis in 1948. These were treated in an orthopaedic ward without further investigation. In May 1953 the patient was admitted to hospital, with pain of over a year's duration in the left lower chest, and was found to have pseudo-fractures of two ribs and X-ray evidence of osteomalacia. There was no history of diarrhoea or of bulky stools, and a detailed dietetic history gave no evidence of poor diet. The haemoglobin level was 15·2 gm. per 100 ml., and red cells 5,020,000 per c.mm. The marrow was normoblastic, and there was free hydrochloric acid in the gastric juice. The serum-calcium level was 4·2 m.Eq. per litre. The results of the differential test of urinary folic-acid excretion were:

Output after 5 mg. given subcutaneously: 2·52 mg.
after 5 mg. given orally: 0·33 mg. } R = 13·1 per cent.

The diagnosis of intestinal malabsorption was confirmed by a fat-balance test, which showed 85 per cent. and 74·6 per cent. absorption in two four-day collections.

Comment. This patient had malabsorption of folic acid and fat, but the clinical features were those produced by malabsorption of calcium and vitamin D. There was no evidence of megaloblastic anaemia, and this was presumably because the body-stores of folic-acid substances, partially maintained by the proportion absorbed from dietetic sources, were sufficient to prevent the occurrence of anaemia. In contrast to the results in this case, another patient, who had generalized osteoporosis, with pseudo-fractures of the right fibula and left femur and several rib fractures, was found to have normal absorption of pteroylglutamic acid. The biochemical findings, which included a calcium-balance test over a period of 10 days, enabled a diagnosis of hyperparathyroidism to be made.

Case 29. A 45-year-old British woman was admitted with pain in the right thigh on walking. There was a previous history of radiotherapy for a 'tumour of the throat' in South America seven years previously, but there was no evidence of a recurrence, although residual difficulty in swallowing persisted. In South America, five years before the present admission, there had been an episode of generalized bleeding, for which blood transfusion was given. There had been no recurrence of bleeding. Two years later the patient had been thought to have either pericarditis or a coronary thrombosis. She said that she had not suffered from diarrhoea, but later, when the diagnosis had been made, amended this statement by saying that for many years she had six or seven non-fatty motions daily for about a week every few months. At the time of admission the haemoglobin level was 7·5 gm. per 100 ml., and red cells 4,530,000 per c.mm. The marrow was normoblastic, and there was no deficiency of megakaryocytes or platelets. There was free hydrochloric acid in the gastric juice, and the serum vitamin-B_{12} level was 270 $\mu\mu$g. per ml. The serum-calcium was 4·5 m.Eq. per litre, sodium 133·9 m.Eq. per litre, and potassium 3·52 m.Eq. per litre. The 'prothrombin' time was 19 seconds (control 13 seconds). A differential test of urinary folic-acid excretion gave the following result:

Output after 5 mg. given subcutaneously: 3·90 mg.
after 5 mg. given orally: 0·85 mg. } R = 21·8 per cent.

A barium follow-through examination showed no abnormality other than stasis, ordinary barium and 'micropaque' being employed. The presence of malabsorption was supported by a fat-balance test, which showed 80 per cent. absorption of fat.

Comment. This appears to be a case of idiopathic steatorrhoea with symptoms due particularly to malabsorption of iron, vitamin K, sodium, calcium, and possibly vitamin D. In this case, too, it would appear that there were sufficient folic-acid substances in the body-stores to prevent the appearance of megaloblastic anaemia.

Case 33. A man aged 34 years was admitted to hospital in February 1946, with a two years' history of diarrhoea and painful mouth. He had not been abroad. The stools were seen to be pale and bulky; the total fat in the faeces was reported as 37·3 per cent., 58·1 per cent. being split. The haemoglobin level was 13·3 gm. per 100 ml., red cells 3,230,000 per c.mm., colour index

1·39, packed cell volume 36 per cent., and mean corpuscular volume 111·5 c.μ. The marrow was megaloblastic. A diagnosis of idiopathic steatorrhoea was made, and the patient was treated with folic acid. The patient was seen at the Blood Clinic frequently, and while treated with folic acid he had no sore tongue or diarrhoea; indeed, he complained of constipation. In September 1953, when there were no symptoms and the blood counts showed haemoglobin 11·9 gm. per 100 ml. and red cells 4,150,000 per c.mm., a folic-acid excretion test was done. The results were:

Output after 5 mg. given subcutaneously: 4·59 mg.
after 5 mg. given orally: 2·07 mg. } R = 45·1 per cent.

The serum vitamin-B_{12} level was 140 $\mu\mu$g. per ml. In January 1955 the patient was not feeling so well generally, although he was continuing to take 10 mg. of folic acid daily by mouth. There was still no diarrhoea. The blood levels were haemoglobin 13·8 gm. per 100 ml., red cells 4,590,000 per c.mm., packed cell volume 41·5 per cent., mean corpuscular volume 90·4 c.μ, and mean corpuscular haemoglobin concentration 33 per cent. The marrow was normoblastic. The urinary folic-acid excretion test was repeated, and this time there was evidence of severe malabsorption. The results were:

Output after 5 mg. given subcutaneously: 1·50 mg.
after 5 mg. given orally: 0·43 mg. } R = 28·7 per cent.

This was indeed surprising, as there was no recurrence of diarrhoea, the bowels moving only once daily. A fat-balance test over two four-day periods showed 85 per cent. absorption of fat. A barium follow-through examination showed the intestinal pattern of sprue, and the oral glucose-tolerance test gave a flat curve. The serum vitamin-B_{12} level was 150 $\mu\mu$g. per ml. Within two weeks of the second folic-acid excretion test the patient began to have diarrhoea again, after having been free of it for six or seven years.

Comment. This case illustrates the fact that during a remission of idiopathic steatorrhoea folic-acid absorption may be normal, but may become impaired again even in the early stages of a relapse, before the onset of symptoms.

The studies reported above show that, in 28 out of 30 cases of idiopathic steatorrhoea and related forms of intestinal malabsorption, the urinary output of folic acid after an oral test dose of pteroylglutamic acid was less than 1·6 mg. The test showed a normal degree of absorption in two patients who had been in clinical and haematological remission for several years while receiving folic-acid therapy. In 60 adult control subjects the ratio of the urinary output after an oral dose to that after an injected dose, calculated in the manner described previously, was from 75 per cent. to 150 per cent., whereas in the 30 cases included in Table I it varied from 0·22 per cent. to 49·2 per cent. Essentially, however, the test should be regarded as one of absorption, and, although it is of interest to compare the urinary output of folic acid after injected and oral doses, a satisfactory modification would be to give injections of 15 mg. of folic acid daily for four days to correct any desaturation, and then to measure the urinary output of folic acid after a single oral test dose of 5 mg. It is hoped to publish, as a separate paper, investigations carried out in conjunction with Dr. Constance Ross in Birmingham, which show that malabsorption of folic acid occurs in children with active coeliac disease. Since absorption of folic acid

from the alimentary tract may be very poor (see Case 4, in which only 0·009 mg. was excreted after a 5 mg. oral dose), it would seem reasonable to give the folic acid by injection, at least in the initial stages of the treatment of megaloblastic anaemia due to malabsorption of folic acid. In addition, since malabsorption of vitamin B_{12} may occur, it would appear sensible to supplement initial and maintenance therapy with folic acid by monthly injections of cyanocobalamin. Where megaloblastic anaemia results from malabsorption of the antimegaloblastic substances, it may be difficult during life to establish the exact pathology. For instance, it is sometimes impossible to be certain whether a patient has idiopathic steatorrhoea or tuberculosis of the mesenteric glands. To the well-recognized causes there may perhaps be added two variants, which would explain some of the confusion that occurs in the Americas about the relationship between malnutrition and steatorrhoea:

Cases of atrophy of the small intestine as a direct result of a defective intake of essential food factors in the diet.

Cases of atrophy of the small intestine as a result of deprivation of essential food factors because of malabsorption.

The clinical picture of idiopathic steatorrhoea and related diseases may be protean in its manifestations, according to the deficiencies that predominate. From the point of view of the development of megaloblastic anaemia, however, it is sufficient to classify cases as follows:

Cases of megaloblastic anaemia due to malabsorption of folic-acid substances.

Cases of megaloblastic anaemia due to malabsorption of folic-acid substances and vitamin B_{12}.

Cases of malabsorption of antimegaloblastic substances in which megaloblastic anaemia has not yet developed.

Megaloblastic Anaemia associated with Structural Abnormalities of the Alimentary Tract

It is easy to understand how disease which destroys the intrinsic-factor bearing area in the fundus and upper part of the body of the stomach may lead to megaloblastic anaemia from deficiency of vitamin B_{12}, since intrinsic factor is required for the normal absorption of vitamin B_{12}. If, however, a patient has gastric carcinoma in that region of the stomach, he will probably die from it before megaloblastic anaemia develops, since the growth would have to be large and the organs, particularly the liver, have good stores of vitamin B_{12} and folic-acid substances. The combination of gastric carcinoma with pernicious anaemia will be referred to later, when 'refractory megaloblastic anaemia' is discussed; most authorities consider that there is an increased incidence of gastric carcinoma in patients with pernicious anaemia. Megaloblastic anaemia has been reported after total and partial gastrectomy, and also after gastroenterostomy or other short-circuiting operations, and in association with fistulae and blind or stagnant loops. It also may occur after removal of an extensive section of small intestine. Table II gives particulars of all cases of megaloblastic anaemia from such causes seen by the author during a period of nine years, and also of patients

TABLE II

Patients who have had Gastric Operations or have Developed Fistulae

Case number	Sex	Age (years)	Operation	Time since operation (years)	Reason for operation	Haemoglobin (gm./100 ml.)	Red cells (millions/c.mm.)	Mean corpuscular volume (c.μ)	Marrow	Serum vitamin B_{12} (μμg./ml.)	Fat-absorption (%)	Urinary folic acid (mg.) (a) After 5 mg. subcutaneous	Urinary folic acid (mg.) (b) After 5 mg. oral	$R\left(\frac{b}{a} \times 100\right)$	Diarrhoea
34	F	48	Total gastrectomy	7	Gastric ulcer	7·8	2·01	124	Megaloblastic	..	82	1·29	2·83	219	Yes
35	M	74	Total gastrectomy	4	Gastric cancer	11·0	3·27	89	Megaloblastic	<50	..	1·06	2·10	198	No
36	M	49	Total gastrectomy	2	Gastric cancer	12·1	4·30	85	Normoblastic	<50	..	..	..	..	No
37	M	66	Total gastrectomy	1½	Gastric ulcer	12·3	3·62	98	Normoblastic	100	..	..	..	..	No
38	F	52	Total gastrectomy	2½	Gastric leiomyoma	11·5	4·38	84	..	110	..	..	..	..	No
39	M	60	Total gastrectomy	1½	Gastric ulcer	10·7	3·96	88	Normoblastic	280*	81	2·20	2·46	112	Yes
40	F	68	Partial gastrectomy	6	Gastric ulcer	6·8	1·59	..	Megaloblastic	<50	..	..	..	..	No
41	F	50	Partial gastrectomy	5	Gastric ulcer	11·1	3·04	102	Megaloblastic	90	..	..	..	..	No
42	F	58	Partial gastrectomy	10	Gastric ulcer	8·1	2·32	125	Megaloblastic	110	90	1·75	2·92	167	No
43	F	67	Partial gastrectomy	4	Gastric ulcer	13·6	4·19	88	Normoblastic	140	78	3·60	4·10	114	Yes
44	F	66	Partial gastrectomy	4	Gastric ulcer	13·7	4·91	..	Normoblastic	140	96	4·29	4·26	99	No
45	M	34	Duodeno-jejunostomy	1½	Duodenal ulcer	14·6	4·90	..	Normoblastic	160	74	3·40	2·70	79	Yes
			Partial gastrectomy	1											
46	M	44	Duodeno-jejunostomy	23	Duodenal ulcer	10·2	2·97	111	Normoblastic	165	82	3·53	4·30	122	Yes
			Partial gastrectomy	2											
47	F	18	Partial gastrectomy and oesophagectomy	1½	Portal hypertension	7·8	3·52	85	Normoblastic	170	..	..	..	..	No
48	M	17	Partial gastrectomy	3	Gastric ulcer	13·9	5·1	..	..	200	..	..	..	..	No
49	F	53	Partial gastrectomy	3	Gastric ulcer	11·8	3·8	..	..	250	..	..	..	..	No
50	M	47	Partial gastrectomy	1½	Duodenal ulcer	15·1	5·22	..	Normoblastic	250	..	2·17	2·89	133	No
51	M	50	Partial gastrectomy	4	Duodenal ulcer	14·5	5·10	..	..	270	82	2·16	1·74	81	Yes
52	F	37	Partial gastrectomy	3	Duodenal ulcer	5·0	3·40	..	..	300	..	..	..	..	No
53	M	59	Partial gastrectomy	4	Duodenal ulcer	13·0	5·21	80	..	310	..	..	..	..	No
54	M	42	Gastroenterostomy	18	Duodenal ulcer	4·6	2·20	75	Normoblastic	320	..	..	..	..	No
			Partial gastrectomy	½											
55	F	35	Partial gastrectomy	3	Duodenal ulcer	8·1	4·31	70	..	400	..	..	..	..	No
56	M	66	Partial gastrectomy	4	Duodenal ulcer	11·1	3·84	..	Normoblastic	..	83	0·44	1·92	436	Yes
57	M	49	Partial gastrectomy	5	Duodenal ulcer	12·1	3·90	..	Normoblastic	..	92	3·70	2·14	58	Yes
58	F	58	Gastroenterostomy	22	Duodenal ulcer	11·5	4·61	83	..	<50	..	..	..	..	No
59	F	63	Gastroenterostomy	25	Duodenal ulcer	4·4	3·12	71	Normoblastic	70	..	2·87	2·54	89	No
60	F	73	Gastroenterostomy	8	Duodenal ulcer	5·8	1·66	108	Megaloblastic	75	..	lost	2·31	..	No
61	M	56	Gastroenterostomy	37	Duodenal ulcer	8·7	2·20	117	Megaloblastic	..	..	..	..	..	Yes
62	F	49	Ileo-sigmoid fistula	?25	..	7·4	1·72	..	Megaloblastic	..	..	2·75	1·92	70	Yes

* Although the serum vitamin-B_{12} level was still normal, there was recovered from the stools 79 per cent. of the activity of a test dose of ^{60}Co-labelled cyanocobalamin. This indicated that the patient could not absorb vitamin B_{12} in a normal manner.

without megaloblastic anaemia who had had gastric operations performed and were investigated by the biochemical tests described above. Some of the patients with megaloblastic anaemia were seen before such tests were available. The operations of partial gastrectomy were of the Polya type. Although a number of cases of megaloblastic anaemia are included in Table II, the fact must be stressed that this is a selected group, and that such a development seldom occurs after partial gastrectomy or gastroenterostomy. The rarity of such a sequel has been considered by Blake and Rechnitzer (1953). It will be seen that the megaloblastic anaemia was associated with a low serum vitamin-B_{12} level in cases in which the latter was estimated; in the other patients with megaloblastic anaemia, seen before such estimations were possible, there was indirect evidence of vitamin-B_{12} deficiency, in that there was a haemopoietic response to injections of concentrated liver extract or of cyanocobalamin. In Cases 36, 37, and 59 there was a low serum vitamin-B_{12} level, but the marrow was normoblastic. In Case 58 marrow puncture was not permitted, but the red-cell level was relatively high. It would seem, therefore, that the development of megaloblastic anaemia in such cases may be predicted by estimation of the serum vitamin-B_{12} level. Another matter of interest brought out by Table II is that, unlike the effects of idiopathic steatorrhoea and related conditions, the malabsorption of fat that may occur after operations on the stomach is not necessarily accompanied by malabsorption of pteroylglutamic acid.

It is reasonable to suggest that patients who have total gastrectomy will develop megaloblastic anaemia in due course, and that this will occur when the body-stores of vitamin B_{12}, and perhaps of folic-acid substances, are so depleted that normoblastic blood formation can no longer continue. After partial gastrectomy the factors concerned will be these body-stores, the amount of intrinsic-factor bearing area removed, and possibly the degree of destruction of remaining gastric mucosa by infection or irritant substances. All the patients shown in Table II as having megaloblastic anaemia had histamine-fast achlorhydria. Case 47 was that of a girl who had the lower portion of the oesophagus and upper part of the stomach removed, together with splenectomy, for portal hypertension. It will be of interest to see whether this operation can lead to megaloblastic anaemia. Megaloblastic anaemia very rarely develops after gastroenterostomy, and even less commonly after some other short-circuiting operation or fistula. In the former instance there may, theoretically, be destruction of the intrinsic-factor secreting cells by gastritis arising from the stoma. It is possible that a blind loop may be responsible for destruction of the antimegaloblastic substances, or for production of toxins, and this factor must be considered in attempting to explain the anaemia in this group of conditions. Certainly therapy with cyanocobalamin and folic acid is not always sufficient to restore the blood picture to normal, as is shown by Cases 60 and 62 below. The following examples may be of interest.

Total gastrectomy. Case 36. A man aged 49 years had the operation performed in June 1952 for gastric carcinoma. In June 1954 he felt well, and the haemoglobin was 12·1 gm. per 100 ml., and red cells 4,300,000 per c.mm. The

serum vitamin-B_{12} level was less than 50 $\mu\mu$g./ml. In January 1955 there was no clinical or haematological deterioration apart from glossitis; the haemoglobin was 13·3 gm. per 100 ml., and red cells 4,830,000 per c.mm. The serum vitamin-B_{12} level remained at less than 50 $\mu\mu$g. per ml. In June 1955 the serum vitamin B_{12} was at the same level, and the blood figures were: haemoglobin 14·4 gm. per 100 ml.; red cells 4,870,000 per c.mm.; packed cell volume 43·5 per cent.; mean corpuscular volume 89·3 c.μ.; mean corpuscular haemoglobin concentration 33 per cent. The marrow was normoblastic. There was no suggestion of subacute combined degeneration of the cord or of clinical deterioration.

Comment. This patient had an abnormally low serum vitamin-B_{12} level for a year without the development of megaloblastic anaemia. Presumably, despite this low serum level, there were still sufficient stores of vitamin B_{12}, or perhaps of folic-acid substances, in the body to maintain normoblastic blood formation.

Partial gastrectomy. Case 42. A 51-year-old woman developed hypochromic anaemia three years after partial gastrectomy for gastric ulcer. The haemoglobin level was 4·4 gm. per 100 ml., red cells 2,700,000 per c.mm., and colour index 0·55, and the blood film was that of iron-deficiency anaemia. The diet was satisfactory, there was no obvious source of bleeding, and the stool benzidine test gave a negative result. There was a response to treatment with ferrous sulphate by mouth. The patient did not report back as an out-patient until nine years later, when she had a degree of iron-deficiency anaemia similar to that recorded above. Although she thereafter took ferrous sulphate regularly, her haemoglobin level rose only from 7·3 gm. per 100 ml. to 8·1 gm. per 100 ml., and the red-cell count fell from 3,310,000 per c.mm. to 2,320,000 per c.mm. The colour index was 1·18, packed cell volume 29 per cent., mean corpuscular volume 125 c.μ, mean corpuscular haemoglobin concentration 27·9 per cent. and reticulocytes less than 1 per cent. The marrow was megaloblastic, and fat-balance test showed 90 per cent. fat-absorption. There was histamine-fast achlorhydria, and a barium follow-through examination showed normal function of the stoma and no evidence of disease of the small intestine. A differential test of urinary folic-acid excretion gave the following results:

Output after 5 mg. given subcutaneously: 1·75 mg.
after 5 mg. given orally: 2·92 mg. } R = 167 per cent.

The serum vitamin-B_{12} level was 110 $\mu\mu$g. per ml. Folic-acid absorption as estimated by the above test was therefore normal, and the serum vitamin-B_{12} level was low. It was decided that, although the primary deficiency appeared to be of vitamin B_{12}, treatment with folic acid should be tried, and to this there was a satisfactory response. The patient has been seen at frequent intervals; after two years' continued treatment with folic acid there is no evidence of neurological deterioration, and the blood counts show haemoglobin 12·0 gm. per 100 ml. and red cells 5,070,000 per c.mm. The serum vitamin-B_{12} level is less than 50 $\mu\mu$g. per ml.

Comment. Megaloblastic anaemia developed after partial gastrectomy, and was associated with vitamin-B_{12} deficiency. Treatment with folic acid was satisfactory, and has not led to neurological complications. It is possible that folic-acid therapy continues to be successful because the body-stores of vitamin B_{12} have not been completely exhausted. If the alternative view, that vitamin-B_{12} depletion is complete, be accepted, it must be taken that folic acid is altogether replacing vitamin B_{12} in its haemopoietic activities, and subacute

combined degeneration of the cord has not developed in a patient depleted of vitamin B_{12} for a period of two years.

Gastroenterostomy. Case 60. A 73-year-old woman was admitted to hospital with symptoms of anaemia complicated by cardiac failure. A gastroenterostomy had been performed for a duodenal ulcer eight years previously. The blood levels were: haemoglobin 5·8 gm. per 100 ml.; red cells 1,660,000 per c.mm.; colour index 1·17; reticulocytes 1·8 per cent. The film was similar to that seen in pernicious anaemia, and the marrow was megaloblastic. There was histamine-fast achlorhydria. No neurological abnormalities were present. A barium meal showed that there was a gastroenterostomy with normal function of the stoma, and that part of the barium passed through the duodenum. The blood urea-nitrogen was 24 mg. per 100 ml., and there was no biochemical evidence of liver disease or of hypoproteinaemia. The patient was not myxoedematous. The serum vitamin-B_{12} level was 75 $\mu\mu$g. per ml. Unfortunately the patient was unable to co-operate in the necessary collection of urine for the first part of the differential test of urinary folic-acid excretion, but the output after the 5 mg. dose given orally was normal, namely 2·31 mg. The patient's condition was such that it was necessary to administer a transfusion of two pints of red cells, and then treatment with adequate doses of cyanocobalamin was given, with ferrous sulphate by mouth. There was a satisfactory initial response. After five weeks this treatment was supplemented by folic acid given orally. In spite of maintenance with 100 μg. of cyanocobalamin by injection every week, together with folic acid by mouth in a dosage of 5 mg. thrice daily, the blood levels even after three months did not rise above the following values: haemoglobin 10·4 gm. per 100 ml.; red cells 3,900,000 per c.mm.; packed cell volume 33·5 per cent.; mean corpuscular volume 86·0 c.μ; mean corpuscular haemoglobin concentration 31 per cent.

Comment. It is possible that the anaemia was due not only to deficiency of folic acid, vitamin B_{12}, and iron, but also to deficiency of some other unknown factor or to absorption of 'toxins' from the gastroenterostomy loop. It has been found that in some cases a further operation, to remove the loop, is required to restore the blood counts to complete normality (see Case 62), but this patient was too old and frail for further surgery. In relation to alimentary loops and the effects of operation, the following case is of interest.

Case. 62. A 49-year-old woman was referred in November 1952 for a folic-acid absorption test, as she was considered to be suffering from idiopathic steatorrhoea. The history was that she had been under treatment for pernicious anaemia with liver injections for more than 10 years, but in 1949 a diagnosis of idiopathic steatorrhoea had been made. At that time diarrhoea and glossitis were troublesome and, despite liver injections, the blood levels were: haemoglobin 11·0 gm. per 100 ml.; red cells 2,900,000 per c.mm.; packed cell volume 29 per cent.; mean corpuscular volume 100 c.μ; mean corpuscular haemoglobin concentration 37·9 per cent.; reticulocytes less than 1 per cent. The marrow contained transitional erythroblasts (transitional megaloblasts), and there was histamine-fast achlorhydria. Fat-absorption (two periods of three days) was 80 per cent. There was a response to treatment with folic acid together with liver injections, but it was not possible to raise the haemoglobin level above 12·7 gm. per 100 ml., or the red-cell count above 4,300,000 per c.mm. After two years the patient ceased reporting to her doctor, and when she was referred for the folic-acid absorption test, in November 1952, she had been given folic acid for

three days, having had no treatment for a year. The haemoglobin was 7·4 gm. per 100 ml., and red cells 1,720,000 per c.mm. A differential test of urinary folic-acid excretion gave the following results:

Output after 5 mg. given subcutaneously: 2·75 mg.
after 5 mg. given orally: 1·92 mg. } R = 70 per cent.

This normal result was disturbing, since no patient with idiopathic steatorrhoea in relapse had shown normal absorption of synthetic pteroylglutamic acid. Accordingly permission was obtained from the patient's own consultant for a glucose-tolerance test and a barium follow-through examination. Absorption of glucose was normal, and the barium follow-through showed an ileo-sigmoid fistula. Serum vitamin-B_{12} measurements were not possible at that time. Treatment with folic acid by mouth was continued for a month, and then injections of cyanocobalamin were given for a year. The highest blood levels reached were haemoglobin 12·9 gm. per 100 ml. and red cells 4,350,000 per c.mm., but it was not possible to maintain the counts constantly at this level. In November 1953, despite the continued administration of cyanocobalamin, the blood figures were: haemoglobin 11·7 gm. per 100 ml.; red cells 3,920,000 per c.mm.; and the marrow was normoblastic. Sir James Learmonth closed the ileo-sigmoid fistula, and no disease was found at operation to account for its occurrence. Two months after the operation fat-absorption was 96·5 per cent., and, although no haemopoietic substances had been given for six weeks, the haemoglobin was 14·6 gm. per 100 ml., and red cells 5,240,000 per c.mm. A year later the patient, who had received no further treatment of any sort, was free of symptoms, had gained 21 lb. in weight, and had a haemoglobin level of 15·1 gm. per 100 ml. and a red-cell count of 5,150,000 per c.mm. The packed cell volume was 43 per cent., mean corpuscular volume 83·3 c.μ, and mean corpuscular haemoglobin concentration 35·1 per cent. The serum vitamin-B_{12} level was 240 $\mu\mu$g. per ml.

Comment. This patient showed clinical features similar to those of idiopathic steatorrhoea, but normal absorption of glucose and of pteroylglutamic acid. The anaemia was caused by an ileo-sigmoid fistula. The haemoglobin and red-cell reading could be raised, but not maintained at a normal level, by a combination of refined liver injections and folic acid, or by cyanocobalamin injections alone, but the anaemia was completely cured by closure of the fistula. Since the anaemia was megaloblastic, and it was possible to control it to a certain extent by cyanocobalamin injections, it seems likely that vitamin B_{12}, and perhaps naturally occurring folic-acid substances (as opposed to synthetic pteroylglutamic acid) could not be absorbed normally. Perhaps these substances are absorbed at a lower level of the intestine than the synthetic pteroylglutamic acid. Closure of the fistula, however, cured the anaemia completely, and this result suggests either that other essential factors, normally absorbed lower down in the small intestine, were being destroyed by bacterial action, or that anaemia-producing toxins were being formed by organisms in a stagnant loop.

Megaloblastic anaemias associated with structural abnormalities of the alimentary tract other than those due to specific diseases of the small intestine or mesenteric glands may conveniently be classified as follows:

Following total, or extensive partial, gastrectomy, with consequent loss of intrinsic-factor bearing area.

Due to disease of the stomach destroying the intrinsic-factor bearing area.
Associated with blind or stagnant loops, or small-intestinal diverticula.
Due to gastroenterostomy, where there may be secondary gastritis with consequent damage to the intrinsic-factor bearing area, and possibly a stagnant loop in addition.
Due to other short-circuiting operations or fistulae, where antimegaloblastic substances may by-pass the absorbing area of the small intestine, and where there may be a stagnant loop in addition.
Due to operative removal of an extensive section of small intestine.
Due to a combination of such factors with other causes of megaloblastic anaemia.

Diphyllobothrium Latum Anaemia

The writer has no experience of this condition, which occurs chiefly in Finland. Von Bonsdorff and Gordin (1952) have shown that the parasite in the upper part of the small intestine acquires vitamin B_{12} at the expense of the host. To what extent such cases are instances of true Addisonian pernicious anaemia hastened by infestation, or instances of megaloblastic anaemia due to the worms depriving otherwise normal persons of vitamin B_{12}, is not clear, but in some patients Addisonian pernicious anaemia is excluded because free hydrochloric acid is present. Five cases have been reported in Britain, the most recent by Harland, Humble, and Mann (1950) and Stevenson (1950). Two patients were Finnish, one was Belgian, one Estonian, and one British. The last-mentioned patient had lived in Northern Europe.

Megaloblastic Anaemia of Infancy and Childhood

Although it has been claimed that pernicious anaemia may occur in childhood, the cases that have been recorded were seen before modern methods of investigation were available. In any future case the complete investigation would include measurement of the serum vitamin-B_{12} level, measurement of absorption of folic acid and of labelled vitamin B_{12}, and a gastric biopsy. Very occasionally coeliac disease may lead to megaloblastic anaemia from malabsorption of folic acid. Megaloblastic anaemia of infancy appears to be essentially a condition of nutritional origin, and it may be that the deficiency varies in different countries, and in different infants in the same country. Many of the infants affected suffered from respiratory infections and alimentary disorders. The only cases seen by the writer were in the United States of America. The infants concerned had been receiving the same proprietary brand of dried milk, and the cause was deficiency of folic acid and ascorbic acid. Although all patients respond to folic acid, a few have been reported to respond to cyanocobalamin therapy. On this basis it appears to be possible to classify the cases into:

Those due to primary deficiency of folic acid in the diet, with coincidental ascorbic-acid deficiency.
Those due to vitamin-B_{12} deficiency.
Those due to coeliac disease, with malabsorption of folic acid.

Those due to structural disease of the small intestine, with malabsorption of folic acid (for example, reticuloses).

Megaloblastic Anaemia of Pregnancy and the Puerperium

There seems to be a considerable degree of confusion about this group of megaloblastic anaemias. There is every reason to suppose that most of the cases that occur in the tropics are examples of nutritional megaloblastic anaemia due to deficiency of folic acid, vitamin B_{12}, or both, the disease being aggravated by the requirements of pregnancy. This is not so, however, with many of the patients seen in Great Britain, who have undoubtedly taken a satisfactory diet during and before the pregnancy. We have not yet seen a patient in Britain who would respond to cyanocobalamin injections, although such a response has been reported from the tropics. Moreover, before the isolation of vitamin B_{12} there were numerous instances of a haematological response to injections of refined liver extract in patients with megaloblastic anaemia of pregnancy. Davidson, Davis, and Innes (1942) reported such a response in five out of 16 cases investigated. From India the favourable reports on the use of cyanocobalamin by Patel and Kocher (1950) of Bombay, and by Chaudhuri (1951) of Delhi, have been criticized by Das Gupta (1954) of Calcutta on the grounds that most of the patients were observed for less than three weeks; nevertheless there was a response during this period.

The serum vitamin-B_{12} level has been estimated in 15 cases of megaloblastic anaemia of pregnancy. It was normal in each instance, the figures ranging from 160 to 530 $\mu\mu$g. per ml. (mean 248 $\mu\mu$g. per ml.). In 18 cases of megaloblastic anaemia of pregnancy it has been possible to carry out either a differential test of urinary folic-acid excretion or a measurement of the urinary output of folic acid after a single 5 mg. loading dose. The results are given in Table III. From experience with control subjects suffering from a variety of diseases it is possible to say that, by the method employed here, the urinary output of folic acid after a 5 mg. test dose, whether given by injection or by mouth, should exceed 1·6 mg. It is obvious from Table III that malabsorption of folic acid, in the form of the synthetic pteroylglutamic acid, is not a feature of megaloblastic anaemia of pregnancy. Nevertheless the anaemia in all these patients responded to folic-acid therapy. It is to be noted that it was especially in patients who had been vomiting, or who had been taking a poor diet, that there was a low output of folic acid after the initial test dose. On the other hand three patients (Cases 70, 72, and 73), who had taken a poor diet, had a normal excretion of the substance. Unfortunately, as has already been indicated, a normal output of folic acid in the urine after an injected test dose of pteroylglutamic acid does not exclude folic-acid depletion. Moreover, many patients have had a poor diet, or vomiting and diarrhoea, throughout pregnancy without developing megaloblastic anaemia, whereas others (for example, Cases 74 and 78) were in good circumstances, had not had many pregnancies, ate a normal diet, did not suffer from vomiting or diarrhoea, absorbed pteroylglutamic acid normally, and had a normal serum vitamin-B_{12} level, and yet developed megaloblastic anaemia that responded to

Table III

Patients with Megaloblastic Anaemia of Pregnancy

Case number	*Age (years)*	*Stage of pregnancy or puerperium*	*Free HCl in gastric juice*	*Haemoglobin (gm./100 ml.)*	*Red cells (millions/c.mm.)*	*Serum vitamin B_{12} ($\mu\mu$g./ml.)*	*Urinary folic-acid excretion (mg.)*		*R* $\left(\frac{b}{a} \times 100\right)$	*Notes*
							(a) *After 5 mg. subcutaneous*	(b) *After 5 mg. oral*		
63	27	28th wk., 1st pregnancy	No	11·8	3·85	..	0·25	2·37	948	Vomiting throughout pregnancy
64	27	11 days after birth of 2nd child	No	4·3	1·48	240	0·47	2·34	498	Vomiting throughout pregnancy
65	23	12 days after birth of 2nd child	..	4·9	2·02	180	..	1·26*	..	Vomiting troublesome
66	42	31st wk., 10th pregnancy	No	9·5	3·23	..	1·27	..	..	Diet poor
67	35	37th wk., 3rd pregnancy	Yes	5·5	1·95	..	1·33	..	..	Nausea and diarrhoea throughout pregnancy
68	32	36th wk., 6th pregnancy	Yes	6·1	2·02	180	1·35	2·42	179	Twin pregnancy. Poor diet
69	22	38th wk., 1st pregnancy	Yes	7·4	4·18	..	1·62	2·63	162	Normal diet
70	35	37th wk., 10th pregnancy	Yes	5·9	1·50	250	1·69	..	..	Diet poor
71	37	34th wk., 7th pregnancy	Yes	8·6	3·81	..	2·37	2·59	109	Twin pregnancy
72	29	Incomplete abortion, 7th pregnancy	Yes	6·0	2·87	..	2·38	1·60	67	Diet poor
73	33	38th wk., 10th pregnancy	Yes	8·2	2·12	170	2·40	2·61	109	Diet poor
74	36	11th wk., 3rd pregnancy	Yes	4·9	1·96	160	2·59	2·36	91	Normal diet
75	25	4 days after delivery, 5th pregnancy	Yes	4·6	2·6	..	2·64	2·10	79	Normal diet
76	31	22nd wk., 2nd pregnancy	Yes	9·2	4·47	..	2·65	3·36	127	Normal diet
77	33	37th wk., 2nd pregnancy	Yes	4·2	1·02	160	2·66	..	..	Normal diet
78	31	36th wk., 2nd pregnancy	..	8·0	3·02	170	..	2·8*	..	Normal diet
79	30	25th wk., 2nd pregnancy	Yes	9·9	2·52	260	3·06	3·28	107	Morning sickness troublesome
80	32	34th wk., 2nd pregnancy	No	6·5	2·7	420	..	4·4*	..	Normal diet

* Only an oral test dose was given to these patients.

folic-acid therapy. In the present state of knowledge it is difficult to put forward any satisfactory hypothesis about the aetiology of megaloblastic anaemia of pregnancy other than that advanced previously (Girdwood, 1953*a*, 1954*b*), namely interference with folic-acid metabolism by unknown endocrine or metabolic factors in pregnancy. Cases of megaloblastic anaemia of pregnancy and the puerperium may be classified as follows:

Nutritional megaloblastic anaemia complicated by pregnancy (the former state being due to dietary deficiency of folic acid, vitamin B_{12}, or both). Many of the cases in the tropics, and a smaller proportion of those in temperate climates, appear to belong to this group.

Megaloblastic anaemia of pregnancy due to unknown factors interfering with folic-acid metabolism. (Presumably these may also play a part in some cases of nutritional megaloblastic anaemia complicated by pregnancy.)

Pernicious anaemia complicated by megaloblastic anaemia of pregnancy (see Davidson, Girdwood, and Clark, 1948). Folic-acid therapy will be required in addition to cyanocobalamin.

Pernicious anaemia occurring in a pregnant patient.

Megaloblastic anaemia of idiopathic steatorrhoea and related conditions complicated by pregnancy. (Case 23, Table I, was first diagnosed as megaloblastic anaemia of pregnancy. Steatorrhoea became evident later.)

Macrocytic Anaemia associated with Chronic Liver Disease

The macrocytic anaemia of chronic liver disease is not usually associated with megaloblastic change in the bone-marrow, but the literature is difficult to follow owing to the confusion caused by various authors using different terminologies. In theory such anaemias might be due to deficiency of folic-acid substances or of vitamin B_{12}. Deficiency of the latter may be shown by measurement of the serum vitamin-B_{12} level, and by a response to cyanocobalamin therapy. The only three satisfactorily documented cases in which it can be accepted with reasonable certainty that the hepatic cirrhosis led to vitamin-B_{12} deficiency have been recorded by Movitt (1950). Measurements of the folic-acid content of the blood have not generally been found to be satisfactory, and a therapeutic response to folic acid does not exclude vitamin-B_{12} deficiency as a cause of megaloblastic anaemia. Accordingly, the only way to prove that macrocytic anaemia in cirrhosis of the liver is due to deficiency of folic-acid substances would be to measure the folic-acid content of the liver in an untreated patient *post mortem*. A suitable case has not yet been available in a centre where such tests can be done, but the following case, though not one of megaloblastic anaemia, may be of interest.

Case 81. In September 1947 a 34-year-old patient, previously healthy, was admitted to hospital 11 days after the premature birth of her fourth child. She had jaundice, vomiting, and diarrhoea, and the liver and spleen were enlarged. Liver-function tests indicated severe damage, and a diagnosis of subacute yellow atrophy was made. In January 1951 the patient was readmitted with anorexia and weakness. The complexion was muddy, and the breath smelt of

mercaptan. There was a bilateral extensor plantar response, and biochemical evidence of severe liver damage. The marrow was normoblastic, and the blood levels were: haemoglobin 12·3 gm. per 100 ml.; red cells 3,830,000 per c.mm.; colour index 1·08; packed cell volume 38 per cent.; mean corpuscular volume 99·2 c.μ; mean corpuscular haemoglobin concentration 32·4 per cent.; white cells 9,200 per c.mm.; reticulocytes less than 1 per cent. The patient rapidly became comatose and died. The liver weighed 690 gm., and was small and very nodular. Microscopically the hepatic tissue was broken up into nodules of varying size by bands of connective tissue. In some places wide areas of liver were replaced by connective tissue. There was little semblance of normal lobular structure, the picture being that of post-necrotic scarring. Since no anti-megaloblastic substances had been given, the hepatic content of vitamin B_{12} and of folic-acid substances was measured. The results, by a pancreatin-extraction method, with added sodium cyanide, were: vitamin B_{12}, 41 μg. per 100 gm.; folic-acid substances (as pteroylglutamic acid) 244 μg. per 100 gm. The livers of five patients without anaemia, malignant disease, or hepatic disease contained 50 to 150 μg. of vitamin B_{12} and 220 to 430 μg. of folic-acid substances per 100 gm. In contrast, in one patient who died of untreated pernicious anaemia, no vitamin-B_{12} activity was detected in the liver, and there were 83 μg. of folic-acid substances per 100 gm. It may therefore be said that in this patient, who died of hepatic cirrhosis with anaemia, the content of antimegaloblastic substances per 100 gm. of liver was about the lower limit of normal (as measured in five patients). It should be noted that the total weight of the organ was reduced. Certainly, however, the figures contrast sharply with those obtained in the patient with untreated pernicious anaemia.

Megaloblastic Anaemia associated with Leukaemia

Although in leukaemia and related conditions there is frequently a low output of folic acid after a 5 mg. test dose (Girdwood, 1953*b*, 1954*b*), it is very rare to find megaloblastic anaemia developing. When it does occur, presumably it is because the rapidly multiplying cells utilize and exhaust body stores of folic acid in the course of their development. In chronic myeloid leukaemia, but not in lymphatic leukaemia, monocytic leukaemia, or acute myeloid leukaemia, the serum vitamin-B_{12} level is very much raised (Beard, Pitney, and Sanneman, 1954; Mollin and Ross, 1955). The cause is not known, but it is possible that either vitamin B_{12} or a B_{12}-binding substance may be derived from the granulocytes. The following case of monocytic leukaemia, in which there were two possible causes for megaloblastic anaemia, may be of interest.

Case 82. A 70-year-old man, who for many years had drunk spirits to excess, was admitted to hospital with symptoms of anaemia and cardiac failure. For many years he had been considered to have hepatic cirrhosis and hypertension. Just before admission his doctor had given him an injection of 100 μg. of cyanocobalamin. On examination there was evidence of cardiac failure and of moderate splenic enlargement, but there was no enlargement of the liver or lymph-nodes. There was free hydrochloric acid in the gastric juice. The serum-bilirubin level was 1 mg. per 100 ml., alkaline phosphatase 8 units, cephalin-cholesterol flocculation plus 4, thymol turbidity 2 units, thymol flocculation test negative, albumin 3·69 gm. per 100 ml., and globulin 2·63 gm. per 100 ml. A blood count showed haemoglobin 6·6 gm. per 100 ml., red cells 2,410,000 per c.mm., colour index 0·93, white cells 16,400 per c.mm., and platelets 105,000

per c.mm. Of the white cells 28 per cent. were neutrophils, 34 per cent. lymphocytes, 25 per cent. monocytes, and 13 per cent. immature cells which were difficult to classify. There were six normoblasts per 100 white cells. The marrow contained many atypical monocytes, and also megaloblasts. A further injection of cyanocobalamin did not cause a change to normoblastic blood formation. The patient died suddenly just after admission; *post mortem* there was well-marked portal cirrhosis, and infiltration of the organs with leukaemic cells. The liver, which weighed 1,650 gm., contained 47 μg. of folic-acid substances (as pteroylglutamic acid) per 100 gm., an abnormally low figure.

Comment. This is a case of megaloblastic anaemia due to folic-acid depletion, in which monocytic leukaemia and portal cirrhosis both may have been aetiological factors.

Megaloblastic Anaemia associated with Haemolytic Anaemia

The author has seen only one instance in which the marrow has become megaloblastic in a patient with haemolytic anaemia. This patient, who has been reported by Davidson (1952), developed megaloblastic anaemia during pregnancy. Davidson (1955) has seen a further similar case. In some of the cases of nutritional anaemia in Assam and Burma, mentioned in the earlier part of the present paper, it seemed likely that the haemolysis caused by certain strains of malaria led to megaloblastic anaemia in patients who were already depleted of antimegaloblastic substances.

'*Refractory Megaloblastic Anaemia*'

The terms 'achrestic anaemia' and 'idiopathic refractory megaloblastic anaemia' have been applied to a form of megaloblastic anaemia, with no obvious cause, which has failed to respond to injections of liver extract that had been used successfully in patients with Addisonian pernicious anaemia. In the light of recent knowledge, separate consideration may be given to cases of megaloblastic anaemia not responding to cyanocobalamin and cases not responding to folic acid.

Megaloblastic anaemia not responding to cyanocobalamin. There can be little doubt that some cases of pernicious anaemia in the past appeared to be refractory to liver extracts because, at that time, some extracts did not contain adequate amounts of vitamin B_{12}. For instance, in a case that had been thought by a general practitioner in 1948 to be one of achrestic anaemia, the liver extract used by him contained only 0·25 μg. of vitamin B_{12} per ml. At the present time, however, manufacturers make microbiological assays of their liver extracts, and such non-potent extracts would not be marketed. Apart from these cases, it seems likely that the majority of the patients who did not respond to injections of liver extract or cyanocobalamin were suffering from intestinal malabsorption predominantly affecting folic acid. In fact some patients, whose condition had been labelled idiopathic refractory megaloblastic anaemia, developed overt steatorrhoea later (for example, Case 3, Davidson and Girdwood, 1948). A differential test of urinary folic-acid excretion will rapidly give evidence of malabsorption of folic acid in such cases. The present author has

seen two patients who were under treatment for pernicious anaemia and who ceased to respond to cyanocobalamin therapy after developing extensive gastric carcinoma; the marrow reverted to the megaloblastic state. It is likely that this change was due to superadded folic-acid deficiency. Recently there have been several reports of megaloblastic anaemia, which has not responded to cyanocobalamin injections, developing in patients receiving phenytoin sodium or related drugs. (Hawkins and Meynell, 1954; Chalmers and Boheimer, 1954; Rhind and Varadi, 1954). Such an occurrence may be due to these drugs interfering with folic-acid metabolism; but many patients receive them, and the number reported as having developed megaloblastic anaemia is very small. The following patient received primidone, but not phenytoin.

Case 83. A 41-year-old woman was admitted to hospital in July 1953 with megaloblastic anaemia. In May of that year she had had a miscarriage in the third month of pregnancy. In all she had had five miscarriages and one normal pregnancy. The blood Wassermann and Kahn reactions were negative. Between May and July 1953 the patient lost her appetite, and became very depressed. It was calculated that during that period she ate about 1,200 Calories daily, with 32 gm. of protein. At no time was there diarrhoea. For many years the patient, an epileptic, had taken phenobarbitone, but from January 1953 she took 'mysoline' (5-ethyl-5-phenyl-hexahydropyrimidine-4:6-dione, or primidone) in a dosage of 1 gm. daily, together with phenobarbitone gr. i at night. At the time of admission to hospital the blood levels were: haemoglobin 4·6 gm. per 100 ml.; red cells 1,150,000 per c.mm.; colour index 1·35; packed cell volume 14 per cent.; mean corpuscular volume 121·7 c.μ; mean corpuscular haemoglobin concentration 32·9 per cent.; white cells 5,000 per c.mm.; reticulocytes 3·6 per cent. Five intramuscular injections each of 100 μg. of cyanocobalamin were given, but the marrow remained megaloblastic. No anticonvulsant drugs were given in hospital. A differential urinary folic-acid test done in hospital gave normal results, the figures being:

Output after 5 mg. given subcutaneously: 1·93 mg.
after 5 mg. given orally: 2·54 mg. } R = 131·6 per cent.

The investigation was repeated, and gave similar results. A fat-balance test could not be done, as the patient would not co-operate in eating the diet. A test meal showed free hydrochloric acid in the gastric juice. A glucose-tolerance test showed normal absorption, and a barium follow-through examination with flocculable barium did not show a 'sprue' pattern. There was a satisfactory response to treatment with folic acid in a dosage of 20 mg. daily, the marrow rapidly reverting to the normoblastic state. In December 1953, although the patient had taken no folic acid for two months, the haemoglobin level was 14·0 gm. per 100 ml., and the red-cell count was 5,410,000 per c.mm. Her general practitioner had recommended therapy with 'mysoline' and phenobarbitone in October 1953, the dosage being the same as formerly. The patient's appetite improved greatly, and she gained 45 lb. in weight.

In August 1954 the haemoglobin and red-cell levels remained normal, and the patient did not thereafter report back to hospital as requested. The only drugs taken were 'mysoline' and phenobarbitone, no change being made in the dosage. In March 1955 the patient was admitted to another hospital with megaloblastic anaemia, the haemoglobin being 5·6 gm. per 100 ml. and red cells 1,450,000 per c.mm. Her appetite remained good, and there was no loss of

weight or diarrhoea. The serum vitamin-B_{12} level was normal (160 $\mu\mu$g. per ml.). The marrow remained megaloblastic when 100 μg. of cyanocobalamin was given, but again there was a rapid response to folic-acid therapy.

Comment. A case of megaloblastic anaemia, with a normal serum vitamin-B_{12} level and normal absorption of synthetic folic acid, occurring in a patient receiving treatment with primidone and phenobarbitone. It is probable that the former drug, or the two in combination, interfered with folic-acid metabolism.

Megaloblastic anaemia not responding to pteroylglutamic acid. It has generally been found that all forms of megaloblastic anaemia, whether caused by deficiency of vitamin B_{12} or of folic acid, will respond initially to treatment with folic acid. In time, however, some patients with megaloblastic anaemia due to vitamin-B_{12} deficiency may cease to respond to folic-acid therapy. In recent years the present author has seen two such cases (Girdwood, 1952, 1953*a*). One of these patients was a 23-year-old man with idiopathic steatorrhoea, who developed megaloblastic anaemia. After two years of treatment with folic acid the anaemia ceased to respond to this substance. The marrow remained megaloblastic even when 15 mg. of folic acid was given daily by injection. There was thereafter a prolonged remission with a single injection of 100 μg. of cyanocobalamin. Although the patient was investigated before serum vitamin-B_{12} assays were possible, it seems reasonable to suggest that there was malabsorption both of folic-acid substances and of vitamin B_{12}, and that depletion of the latter became so great that folic-acid therapy ceased to be effective. The other patient, a woman aged 70 years, had pernicious anaemia, which had been treated by her doctor for two and a half years by the oral administration of a proprietary preparation containing folic acid but no cyanocobalamin. No such treatment had been given for six months prior to her admission to hospital. Folic acid was then given, but there was no response, the marrow remaining megaloblastic. A rapid haematological and clinical response occurred when cyanocobalamin was given, and the patient, who has been maintained with cyanocobalamin injections for two and a half years, is in very good health. It has been suggested that, where the primary deficiency is of vitamin B_{12}, folic acid acts by 'mass action' in enzymatic processes concerned with nucleic-acid metabolism. It might be argued further that folic acid will prevent megaloblastosis as long as traces of vitamin B_{12} remain available, and that this in turn depends on how absolute the deficiency of intrinsic factor may be. The last-mentioned case may be one in which vitamin-B_{12} deficiency was particularly complete. More cases of this type might have been seen if, after the synthesis of pteroylglutamic acid in 1945, treatment of many sufferers from pernicious anaemia with folic acid alone had been continued for several years. That this was not done was due to recognition of the fact that folic-acid therapy does not afford protection against the development of subacute combined degeneration of the cord. It is a matter of some interest that, in contrast to another patient (Case 3), who had neurological complications associated with vitamin-B_{12} deficiency without showing a truly megaloblastic marrow, the two patients referred to above seemed to have megaloblastic anaemia due to total

exhaustion of body-stores of vitamin B_{12}, and yet did not have either subjective or objective neurological manifestations.

Cases of 'refractory' megaloblastic anaemia without obvious cause may therefore be classified as follows:

Cases of megaloblastic anaemia not responding to cyanocobalamin injections:

Due to defects in the cyanocobalamin or refined liver extracts. We have seen deterioration occur in one highly potent liver extract after it had been kept at room temperature for six months. This is unusual.

Due to unsuspected intestinal malabsorption of folic acid.

Due to extensive carcinoma of the stomach, leading to folic-acid deficiency.

Due to administration of phenytoin sodium, primidone, and perhaps other anticonvulsant drugs.

Cases of megaloblastic anaemia not responding to pteroylglutamic acid:

Due to prolonged treatment with pteroylglutamic acid of patients in whom the primary deficiency is of vitamin B_{12}, and is absolute or nearly complete.

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Summary

1. From experience of over a thousand cases of megaloblastic anaemia, the more recent of which were investigated by a differential test of urinary folic-acid excretion and a serum vitamin-B_{12} assay, a classification of the megaloblastic anaemias is suggested.

2. The nutritional megaloblastic anaemias require investigation by modern means. They comprise a complex group of diseases, with multiple aetiological factors which vary in relative importance in different geographical areas.

3. In the pernicious anaemia group, the serum vitamin-B_{12} estimation is of particular value as an aid to diagnosis where neurological changes draw attention to the condition before megaloblastic anaemia develops.

4. Malabsorptive diseases such as idiopathic steatorrhoea may be protean in their clinical features. The condition may manifest itself, for example, as multiple fractures without anaemia, generalized bleeding from vitamin-K deficiency, or iron-deficiency anaemia refractory to treatment with iron by mouth. Diarrhoea is not necessarily present, and a fat-balance test carried out over a short period of eight days and referred to a routine laboratory may not

reveal the disorder. In such cases measurement of folic-acid absorption and subsequent urinary excretion is of particular value. The test has been positive in 28 out of the 30 cases of idiopathic steatorrhoea and related conditions investigated. The other two patients had been without symptoms for many years.

5. After total or partial gastrectomy, or after gastroenterostomy, megaloblastic anaemia may develop as a result of vitamin-B_{12} deficiency, but lowering of the serum vitamin-B_{12} level may occur several months before megaloblastic anaemia develops. It is possible that, for a certain time, bodily stores of folic-acid substances are able to maintain normoblastic blood formation where there is depletion of vitamin B_{12}. Unfortunately there is as yet no satisfactory method for measuring the body-stores of folic-acid substances. In this group of patients absorption of the synthetic folic acid is normal.

6. Where blind or stagnant loops are present, there may be megaloblastic anaemia which can be controlled by cyanocobalamin or folic acid, but operative removal of the loop may be necessary to restore the blood counts and the general health to normal.

7. The megaloblastic anaemias of pregnancy and the puerperium probably constitute a special group. In the tropics nutritional megaloblastic anaemia complicated by pregnancy is no doubt the common form. In Britain the serum vitamin-B_{12} level is generally normal, and it is likely that in some such cases unknown factors of pregnancy interfere with folic-acid metabolism. Absorption of synthetic folic acid is normal.

8. A report is given of one case of anaemia, due to chronic liver disease, in which the hepatic content of folic acid and vitamin B_{12} was not greatly reduced. The marrow was not, however, megaloblastic.

9. The terms 'achrestic anaemia' and 'idiopathic refractory megaloblastic anaemia' have, in the past, probably been used for cases in which there was no response to cyanocobalamin injections because the defect lay in absorption of folic-acid substances. Other reasons for a lack of response to cyanocobalamin in megaloblastic anaemia are given.

10. A report is given of an epileptic patient who developed megaloblastic anaemia on two occasions while being treated with primidone and phenobarbitone. Unlike other reported cases, she had not received phenytoin.

11. Megaloblastic anaemia may fail to respond to folic acid in patients who have already had prolonged treatment with folic acid, and in whom vitamin-B_{12} deficiency is absolute or nearly complete.

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THE NATURAL HISTORY OF PULMONARY COLLAPSE IN CHILDHOOD[1]

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Existing reports of pulmonary collapse in childhood have dealt mostly with selected groups of cases. It was decided, therefore, to obtain an overall view of the problem by reviewing the course of every known case of pulmonary collapse encountered at the Princess Louise Hospital for Children in the years 1945 to 1952. Our purpose was to try to evaluate the importance of the various aetiological factors, to review the course of the disease, and to obtain information concerning prognosis. The criteria for inclusion in the survey were in the first place radiological, and accordingly all chest radiographs for the period 1945 to 1952 were reviewed for evidence of pulmonary collapse. From the radiographs of almost 5,000 children, 854 were agreed by all three authors to show evidence of pulmonary collapse. Of these 854 patients accepted for the survey, 472 were examined at the survey follow-up clinic.

Radiology of Pulmonary Collapse

Patients included in this survey are those in whom a diminution in size of one or more bronchopulmonary segments was clearly demonstrable radiologically. In the majority of our cases partial collapse only had occurred, the collapsed segment or lobe being clearly visible as an opaque shadow on X-ray, but diminished in size from the normal, the appearance being that which is commonly described as 'collapse-consolidation'. In the minority of the patients complete collapse of a segment or lobe had occurred. In such cases the only evidence of pulmonary collapse in plain radiographs was often an alteration in vascular pattern of the remaining lung tissue, together with a thickening of the pleural fissure at the site of the collapsed segment or lobe. Where doubt existed, bronchography was carried out to confirm the presence of pulmonary collapse. Throughout the period of the survey anteroposterior and right lateral radiographs of the chest were taken at each examination, but in some older children postero-anterior films were taken. Towards the end of the survey, however, in the absence of knowledge of an existing lesion, a change was made in the routine examination from the right to the left lateral X-ray, since a better view of the lung bases, clear of both diaphragm shadows, was thereby obtained. We refer throughout to the lingular lobe as functionally separate, although anatomically, and according to the pleural reflections, it is a segment of the

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left upper lobe. With this exception the standard nomenclature of broncho-pulmonary anatomy accepted by the Thoracic Society has been used.

Aetiology

The 854 children were divided into 10 groups according to the aetiology of the collapse (Fig. 1). Collapse following pertussis, measles, asthma, tuberculosis,

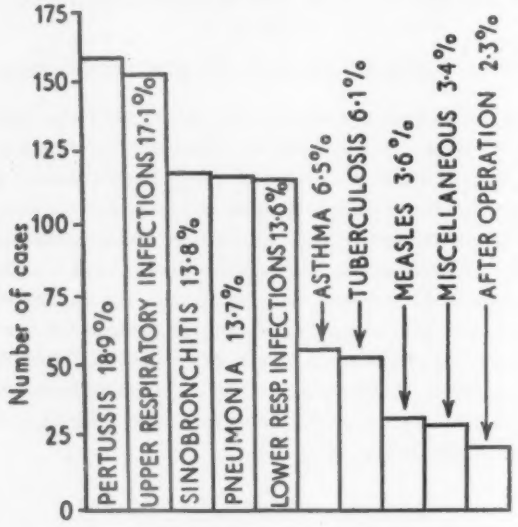

FIG. 1. Aetiology of pulmonary collapse in 854 consecutive cases.

TABLE I

Diagnosis between Sinobronchitis, Upper Respiratory Infections, Lower Respiratory Infections, and Pneumonia

	Antral infection		*Lower respiratory signs*				*Nasal catarrh*	
	Acute	*Chronic*	*Tonsillitis*	*Collapse consolidation*	*Bronchitis*	*Acute respiratory distress*	*Acute*	*Chronic*
Sinobronchitis	+	+	±	−	+	−	+	+
Upper respiratory infections	±	−	±	−	−	−	+	−
Lower respiratory infections	−	−	−	−	+	−	±	−
Pneumonia	−	−	−	+	±	+	−	−

and anaesthesia presented no difficulty in diagnosis, but the differentiation between sinobronchitis, upper respiratory infections, lower respiratory infections, and pneumonia was much more complex. We are aware of the difficulties inherent in retrospective study of clinical records, but nevertheless believe that

we have been able to obtain a valid separation of these four groups. Sinobronchitis was characterized by chronicity, that is, the presence of chronic antral infections, persistent purulent nasal discharge, and bronchitis, whereas children with upper respiratory infections had acute nasal catarrh or tonsillitis without signs of bronchitis or pneumonia. The children with collapse accompanying or following pneumonia all presented acute respiratory distress, in some cases with acute nasal catarrh, and clinical and radiological evidence of collapse-consolidation. The group with lower respiratory infections consists of those patients who had bronchitis, unaccompanied by acute respiratory distress, signs of consolidation, sinusitis, or tonsillitis. The differential diagnosis is shown in Table I.

General Incidence and Methods of Classification

Table II shows the incidence of collapse in each aetiological group, as it occurred in the different lobes either singly or in combination. The age incidence and recurrence rate are also recorded. Table III is concerned with the 472 children seen by us at the follow-up clinic. In 422 patients re-expansion of the lung had taken place, and the duration of the collapse is recorded. The remaining 50 patients had persistent collapse. The length of time for which collapse had been present in this group varied (see the section on persistent collapse) but was never less than two years. The age incidence, aetiology, and lobar distribution, in all the patients who were followed up and showed persistent collapse at the termination of the survey, are also recorded in Table III.

Description of Aetiological Groups

Sinobronchitis is a frequent cause of persistent cough, associated with recurrent upper respiratory infections and protracted, intermittent, low-grade fever in childhood. Price (1951) analysed 126 cases, but mentioned atelectasis as occurring only twice. He found bronchiectasis in five cases, but made no reference to any preceding collapse. Egbert (1942) gave a clinical description of sinobronchitis with atelectasis preceding bronchiectasis, and Oswald (1946–7) collected 50 cases of collapse of the lower lobes in children, but in only one case did he incriminate infected antra, although he found infections of the nose and throat, especially infected sinuses, in 16 cases. In our group of cases of sinobronchitis we include only those children who had clinical evidence of chronic sinusitis, and in whom, with few exceptions, antral opacity was confirmed radiologically. In each case there was a long history of persistent or recurrent purulent nasal discharge, associated with recurrent episodes of bronchitis or collapse. Bronchoscopy was undertaken in five patients, revealing in each case bronchial oedema and muco-pus within the affected bronchus. In no case did the lung re-expand speedily after bronchoscopy, and this finding is in agreement with that of most observers, who have reported that bronchoscopy is of therapeutic value only in the very early stage of acute collapse. Eighty patients were seen at the follow-up clinic, and 16 of these (20 per cent.) were found to have persistent collapse.

TABLE II

Data affecting 854 Children with Pulmonary Collapse

	Sino-bronchitis	*Upper respiratory infections*	*Lower respiratory infections*	*Pneu-monia*	*Pertussis*	*Measles*	*Asthma*	*Tuber-culosis*	*After operation*	*Miscellaneous*	*Total*
Number of cases	118	154	116	117	161	31	56	52	20	29	854
Percentage	*13·8*	*17·1*	*13·6*	*13·7*	*18·9*	*3·6*	*6·5*	*6·1*	*2·3*	*3·4*	*100*
Total lobar incidence											
Right middle	61	42	36	29	90	17	26	23	5	7	336
Right lower	33	50	36	27	47	6	15	11	1	10	236
Right upper	12	16	18	34	12	3	10	17	4	7	133
Lingular	23	15	14	8	50	9	12	4	2	4	141
Left lower	60	74	65	47	82	17	10	7	8	14	384
Left upper	4	5	3	6	0	3	4	3	0	4	32
Lobar incidence in isolated lobe collapse											
Right middle	23	28	10	13	29	5	17	14	4	4	147
Right lower	15	29	7	13	24	5	12	11	0	3	119
Right upper	5	4	1	11	2	0	4	8	1	2	38
Lingular	2	5	2	2	6	0	6	3	0	0	26
Left lower	18	46	35	30	20	9	7	5	2	9	181
Left upper	1	0	1	6	0	0	0	1	0	0	9
Number of lobes affected in initial attack											
One	64	112	56	75	81	17	47	42	16	18	528
Two	40	36	50	24	60	7	7	10	2	7	243
Three	10	6	8	14	15	5	2	0	2	3	65
Four	4	0	2	1	4	1	0	0	0	0	12
Five	0	0	0	3	1	1	0	0	0	1	6
Age incidence											
Under 1 year	3	18	13	23	15	3	3	7	1	20	106
1–2 years	12	21	19	19	15	3	7	7	1	2	106
2–5 years	41	58	30	39	72	13	24	17	3	5	302
Over 5 years	62	57	54	36	59	12	22	21	15	2	340
Total recurrences	30	15	13	9	12	1	14	3	0	0	97
Recurrence rate %	*25·4*	*9·7*	*11·2*	*7·6*	*7·4*	*3·2*	*25*	*5·7*	*0*	*0*	*11·3*
Recurrences with same aetiology as initial collapse	27	12	8	4	1	0	14	3	0	0	69
Recurrence rate %	*22·8*	*7·8*	*6·9*	*3·4*	*0·6*	*0*	*25*	*5·7*	*0*	*0*	*8·1*

		After operation		*Miscellaneous*		*Total*	
Number of ca		13		9		472	
		Number	%	*Number*	%	*Number*	%
1. Lung re-expanded at follow-up examination							
Duration of collapse	Under 3 months	12	92·3	8	88·9	240	50·85
	3–6 months	1	7·7	1	11·1	59	12·5
	6–9 months	0	..	0	..	31	6·6
	9–12 months	0	..	0	..	23	4·9
	1–2 years	0	..	0	..	14	3
	Over 2 years	0	..	0	..	3	0·6
	Unknown	0	..	0	..	52	11
2. Persistent collapse:							
Total cases		0	..	0	..	50	10·6
Age at onset	Under 1 year	0		0		3	
	1–2 years	0		0		7	
	2–5 years	0		0		15	
	Over 5 years	0		0		25	
Lobar incidence	Right middle	0		0		19	(10·6%)*
	Right lower	0		0		10	(6·4%)
	Right upper	0		0		7	(12·7%)
	Lingular	0		0		14	(15·2%)
	Left lower	0		0		13	(6·3%)
	Left upper	0		0		2	(12·5%)

TABLE

Data affecting 472 Children with Pulmonary Co

'Persistent collapse' has been p

		Sinobronchitis 80		*Upper respiratory infections* 82		*Lower respiratory infections* 38		*Pneumonia* 67		*Pertu* 105
Number of cases		*Number*	%	*Number*	%	*Number*	%	*Number*	%	*Number*
1. Lung re-expanded at follow-up examination										
Duration of collapse	Under 3 months	32	40	44	53·7	20	52·6	52	77·6	45
	3–6 months	11	13·75	5	6·1	4	10·5	3	4·5	27
	6–9 months	7	8·75	6	7·3	3	7·8	0	..	10
	9–12 months	7	8·75	1	1·2	2	5·25	0	..	5
	1–2 years	3	3·75	1	1·2	0	..	0	..	5
	Over 2 years	1	1·25	0	..	1	2·6	0	..	0
	Unknown	3	3·75	21	25·6	5	13·2	9	13·5	8
2. Persistent collapse:										
Total cases		16	20	4	4·9	3	7·8	3	4·5	5
Age at onset	Under 1 year	0		0		0		1		0
	1–2 years	2		1		0		1		1
	2–5 years	4		1		1		1		1
	Over 5 years	10		2		2		0		3
Lobar incidence	Right middle	7		0		3		0		4
	Right lower	2		3		0		1		2
	Right upper	0		0		0		0		0
	Lingular	7		0		0		1		1
	Left lower	3		1		1		0		2
	Left upper	0		0		0		1		0

* Figures in parentheses are percentage persistence among all c

E III

Collapse who attended Follow-up Examination

present for two years or longer

rtussis 05		*Measles* 18		*Asthma* 32		*Tubercu-losis* 28		*After operation* 13		*Miscellaneous* 9		*Total* 472	
ber	%	*Number*	%	*Number*	%	*Number*	%	*Number*	%	*Number*	%	*Number*	%
42·9		7	38·8	18	56·25	2	7·1	12	92·3	8	88·9	240	50·85
25·7		4	24·4	1	3·1	2	7·1	1	7·7	1	11·1	59	12·5
9·5		2	12·2	1	3·1	2	7·1	0	..	0	..	31	6·6
4·8		2	12·2	3	9·4	3	10·7	0	..	0	..	23	4·9
4·8		0	..	1	3·1	4	14·3	0	..	0	..	14	3
..		0	..	1	3·1	0	..	0	..	0	..	3	0·6
7·6		1	6·1	4	12·5	1	3·5	0	..	0	..	52	11
4·8		2	11	3	9·4	14	50	0	..	0	..	50	10·6
		0		0		2		0		0		3	
		0		0		2		0		0		7	
		0		2		5		0		0		15	
		2		1		5		0		0		25	
		1		2		2		0		0		19	(10·6%)*
		1		0		1		0		0		10	(6·4%)
		1		0		6		0		0		7	(12·7%)
		2		1		2		0		0		14	(15·2%)
		2		1		3		0		0		13	(6·3%)
		0		0		1		0		0		2	(12·5%)

ll cases followed up in which collapse of the lobe had occurred.

Upper respiratory infection. Thirty-nine children in this group of 154 had acute tonsillitis, and they have been compared with the other 115 who had acute nasal catarrh without chronic antral or acute tonsillar infection. The age incidence, number and pattern of lobes affected, and duration of collapse are similar in these two sub-groups; but, of the 82 children who attended the follow-up clinic, persistent collapse was found in three (15 per cent.) of the 20 who had had tonsillitis, compared with only one (1·6 per cent.) of the other 62. Although these numbers are too small to be significant, the trend may be worthy of further study, and emphasizes the need for early diagnosis and treatment in such cases.

Lower respiratory infection. In the initial review of our total series it became apparent that there were a number of patients who suffered from respiratory infection with fever, malaise, and cough, with signs of generalized or localized bronchitis. For the purposes of classification we have described these cases as 'lower respiratory infection'. Many authors, for example, Campbell, Strong, Grier, and Lutz (1943), Correll and Cowan (1943), Kay (1945), and Scadding (1948), have drawn attention to the collapse which is associated with primary atypical pneumonia, and they attributed it to local and inflammatory oedema of bronchi and bronchioles. Robertson and Morle (1951) described a series of adults with 'primary atypical pneumonia', and believed the cause to be aspiration of the mucous products of upper respiratory infection. The illness varied in intensity and duration, and there were minimal signs of upper respiratory infection, with generalized signs of bronchitis. 'Some degree of collapse within the lesion was very frequent.' This picture is very similar, both clinically and radiologically, to that found in the children whom we have placed in this group. Persistent collapse was present in only three of the 38 patients followed up (7·8 per cent.), but bronchography did not reveal bronchiectasis.

Pneumonia. The children in this group were acutely ill, with signs of consolidation and respiratory distress, and radiologically there was evidence of collapse associated with consolidation. Three patients out of 67 at the follow-up clinic had persistent collapse (4·5 per cent.). Bronchography in two of these patients revealed partial collapse, but no bronchiectasis.

Pertussis. The children with post-pertussis collapse were often seen several weeks after the height of the illness, and a typical history was accepted as evidence of the infection. Persistent collapse was seen in five patients (4·8 per cent.). Bronchoscopy was carried out in four patients, but in none did re-expansion occur sooner than six months later. Although the incidence of persistent collapse was low, bronchography revealed bronchiectasis in two out of the five patients in whom it was found. Nicholson (1949) and Lees (1950) have both analysed series of cases of pertussis, and Fig. 2 shows a comparison between their cases and ours as regards the lobar incidence. The striking difference is the much higher incidence of right middle lobar and lingular collapse in our series, for which there is no apparent reason, unless lateral radiographs were not taken in all the cases recorded by the other authors. Nicholson stated that re-expansion of collapse is unlikely to occur after nine months, and Lees believed that surgical removal of a collapsed lobe should not be undertaken less than one

year from the onset. In five of our patients expansion occurred after an interval of between one and two years and, in view of our figures relating to this and other groups, it would seem that surgery should not be undertaken for at least two years, or possibly longer.

Measles. Post-measles collapse was characterized by multiple lobe involvement and, although only two patients out of the 18 seen at the follow-up clinic

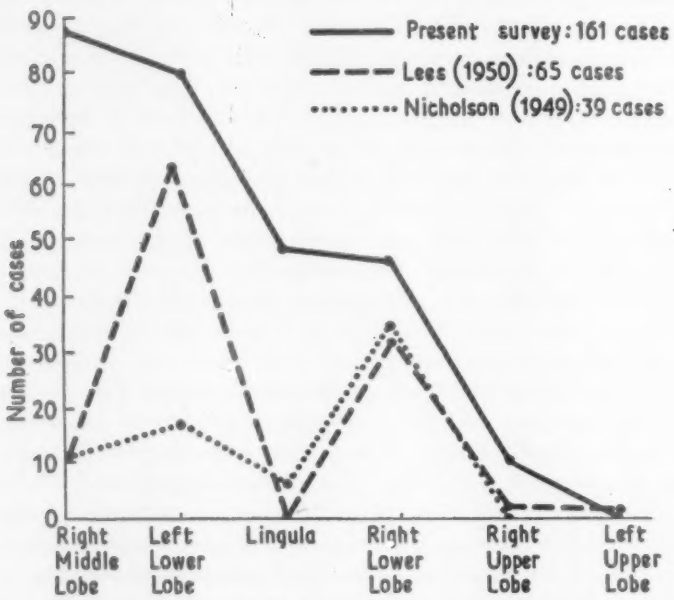

FIG. 2. Pertussis. Comparison of lobar incidence of collapse in the present survey and as recorded by Lees (1950) and Nicholson (1949).

showed persistent collapse (11 per cent.), bronchography revealed widespread bronchiectasis in each.

Asthma. The children did not have X-rays taken during each attack of asthma, but usually only when the attack merited admission to hospital or attendance at the out-patient clinic shortly afterwards, therefore the recurrence rate of 25 per cent. is almost certainly an underestimation. Three out of the 32 patients followed up showed persistent collapse (9·4 per cent.), but bronchography did not reveal bronchiectasis.

Tuberculosis. Children in this group were seen in the initial stages of their illness, before transfer to a sanatorium or to outpatient surveillance at a chest clinic. Twenty-eight patients were seen at the follow-up clinic, 14 (50 per cent.) showing persistent collapse. Most of the patients were under the care of other physicians or clinics, and in the majority bronchographic examination was not carried out during the period of the survey. The recent work of Thomas (1952) has shown, in long-term observation combined with bronchoscopic and bronchographic study, the high incidence of bronchiectasis, and of phthisical lesions

of the adult type, occurring later in children who have primary tuberculous lesions, with complications, in the chest. The number of patients in our follow-up group is too small, and our investigation of them too incomplete, to warrant definite conclusions, but our findings tend in all respects to support his observations. With regard to the anatomical distribution of pulmonary collapse in primary tuberculous lesions, Macpherson and Lutwyche (1950) found that the right upper lobe and right middle lobe were less frequently involved than the left upper lobe and right lower lobe. This is in opposition to our findings, in which the right middle lobe or the right upper lobe, or both, were involved in 76·9 per cent. of cases, and to those of Graham and Hutchison (1947), who found a high incidence of collapse in these lobes. This preponderance of collapse in the right middle and upper lobes was explained on an anatomical basis by Brock, Cann, and Dickinson (1937), on the grounds that the bronchopulmonary gland lying below the eparterial bronchus, in the angle between it and the right lower bronchus, is likely, if diseased, to distort and obstruct the orifices of the right upper- and middle-lobe bronchi.

Pulmonary collapse after operation. In this group of 20 patients re-expansion occurred in less than 21 days in 19 cases, and between three and six months in one case.

Miscellaneous group. Twenty-nine cases fell into this category. Eight children had pleural effusion associated with pneumonia; four had aspiration pneumonia, two after convulsions and two as a result of choking during feeds; one baby had a diaphragmatic hernia, and subsequently died; one child had ulcerative stomatitis; nine babies, all of whom died, had fibrocystic disease of the pancreas; and six cases were unclassified. Nine of the 29 patients in this group attended the follow-up clinic, and in none did we find persistent collapse.

Discussion

I. An attempt was made to distinguish the lobar pattern of collapse due predominantly to intrabronchial obstruction by aspirated secretions from that of collapse due to extrabronchial compression by enlarged glands.

Collapse predominantly due to aspiration. Quinn and Meyer (1929) and McLaurin (1935) showed the ease with which material from the nose and sinuses is aspirated into the lungs. Goodwin (1934) reviewed cases of lipoid pneumonia secondary to aspiration of oily substances, and found the right lung more often affected than the left, the upper lobes more often than the lower lobes, and the posterior segments of the lung more often than the anterior. Fig. 3 shows that lower respiratory infections, upper respiratory infections, and pneumonia affect the lobes in the same order of frequency, with the exception that pneumonia, more than the other two groups, shows a predilection for the right upper lobe. Sinobronchitis, surprisingly, conforms more closely to the lobar pattern of pertussis, measles, and asthma (Fig. 4). Among these diseases, however, asthma shows a low incidence of collapse of the left lower lobe. Comparison of these groups of cases shows that it is not possible to determine a definite lobar pattern

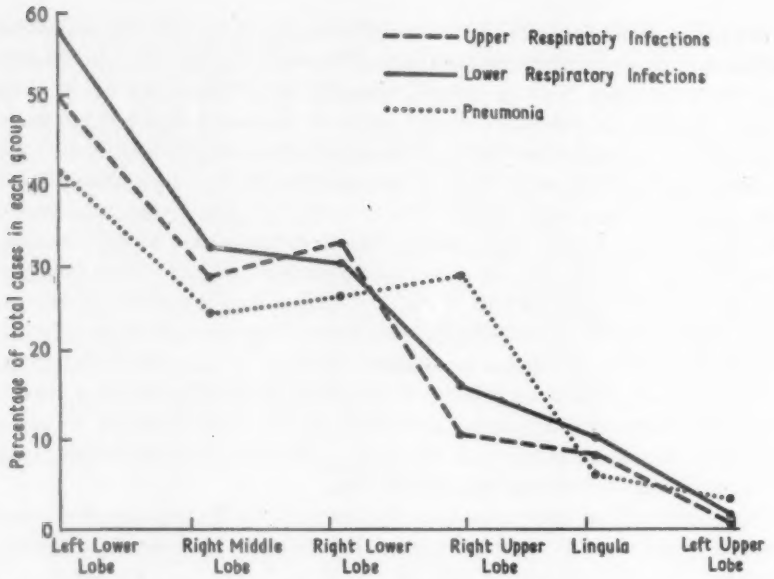

FIG. 3. To show the numerical relationship of lobes affected in upper respiratory infections, lower respiratory infections, and pneumonia.

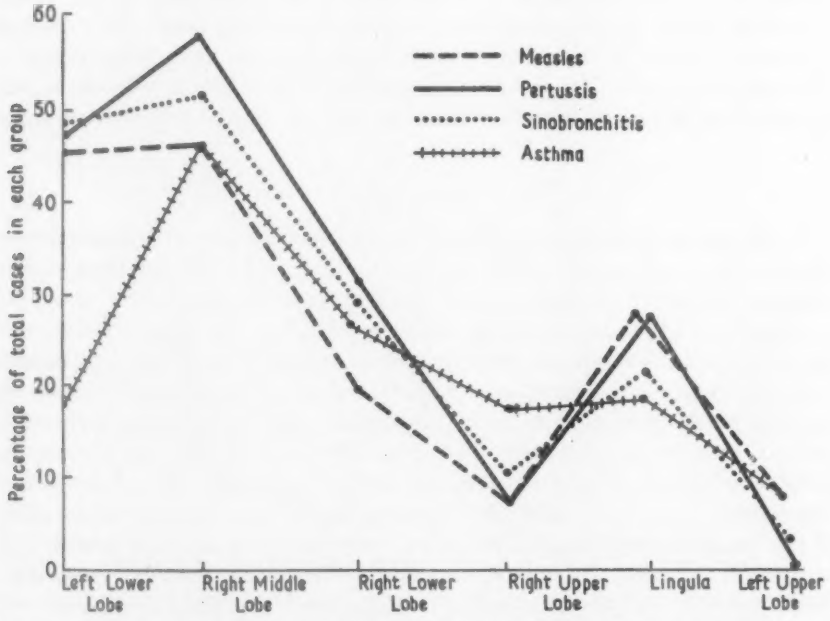

FIG. 4. To show the numerical relationship of lobes affected in asthma, sinobronchitis, pertussis, and measles.

of aspiration atelectasis, but we have found that the incidence of collapse in the lower lobes is high, and that in all groups, except asthma, collapse of the left lower lobe predominates. The high rate of collapse of the right middle lobe in sinobronchitis is unexplained. Schenck and Seldowitz (1952) found radiological evidence of hilar and mediastinal lymphadenopathy among their 168 cases of sinobronchitis, but they recorded neither the site nor the incidence of collapse. We did not find radiological evidence of enlarged glands in the chest except with primary tuberculosis, and we are also unable to account for the frequent involvement of the right middle lobe in asthma and measles.

Collapse predominantly due to hilar glandular enlargement. Collapse of the right middle and upper lobes is said to be common where glandular enlargement is prominent (Brock, Cann, and Dickinson, 1937). Study of the tuberculous cases in our series illustrates this point, and is in conformity with recent bronchoscopic studies of primary tuberculosis in childhood (Hutchison, 1949; Daly, Brown, Lincoln, and Wilking, 1952). The right middle lobe was affected in 58 per cent. of our post-pertussis cases and, although there may be marked hilar and mediastinal lymphadenopathy in the first two or three weeks of the illness, it is generally believed that the atelectasis is associated with the abundant viscid bronchial secretion which is invariably found in pertussis. Glandular compression may, however, play an early part in causing the collapse, which is then accentuated and perpetuated by the increased secretion.

II. *The 'middle lobe syndrome'*

Considerable attention has been given recently to the existence of a 'middle lobe syndrome' (Paulson and Shaw, 1949; Harper, Condon, and Weirman, 1950; Rubin and Rubin, 1950; Graham, Burford, and Mayer, 1948; Kross and Rosenblatt, 1951). From these reports the so-called middle lobe syndrome emerges as a clinical condition resulting from bronchial obstruction by persistently enlarged lymphatic glands. The obstruction gives rise to the pulmonary changes of collapse, infection, and bronchiectasis distal to the persistently distorted and, later, constricted bronchus. The initial glandular enlargement may be due to tuberculosis or other infective causes. Any bronchus may become thus distorted, but the anatomical distribution of the hilar glands makes the right middle lobe particularly vulnerable. The main clinical features—repeated haemoptyses, recurrent pulmonary infections, and chronic cough with a variable amount of sputum—remain constant whichever lobe is affected. Among our own series of 472 children seen at the follow-up clinic, 27 patients with persistent collapse known to have been present for over three years are included:

Tuberculosis	8 cases
Sinobronchitis	10 „
Pertussis	3 „
Pneumonia	2 „
Measles	2 „
Lower respiratory infection without consolidation	1 „
Asthma	1 „

Their clinical condition was reviewed for evidence of symptoms said to be characteristic of the 'middle lobe syndrome'. Of these 27 patients only 11 had a history of recurrent respiratory infections or of persistent cough with sputum. In our entire series only a few children, in the acute phase of pertussis, had haemoptysis. The remaining 16 children in this group were free from symptoms, in spite of the length of time that pulmonary collapse had persisted. Six of the patients presenting symptoms had a single lobe involved, and the remaining five had collapse of two or more lobes. It is of interest to note that there were eight cases of tuberculosis in this group of children in whom collapse had been present for three years or longer, and in these cases the middle lobe was involved only once. Moreover, none of these tuberculous children had any residual symptoms. We saw no typical case of the 'middle lobe syndrome' in the entire series.

III. *Isolated lobar collapse*

When a single lobe was affected, the collapse involved one or more segments more often than the whole lobe. The exceptions to this finding were the right middle and lingular lobes (Fig. 5). The aetiological incidence and distribution were found to be similar whether the whole or only part of the lobe was involved; segmental and lobar collapse are therefore considered together in the following section.

The occurrence of isolated collapse of a particular lobe (expressed as a percentage of the total incidence of collapse of the lobe) was: right lower lobe, 52 per cent.; left lower lobe, 47 per cent.; right middle lobe, 43 per cent.; right upper lobe, 28 per cent.; left upper lobe, 28 per cent.; lingular lobe, 18 per cent. It will be seen that isolated collapse of the lingular lobe is infrequent, perhaps because it is so often collapsed in association with the left lower lobe. Isolated collapse of the upper lobes is unusual except in pneumonia and tuberculosis, and these lobes tend to become involved when the more commonly affected lobes are also implicated. Fig. 6 shows the percentage of cases of collapse of an isolated lobe arranged according to aetiology. The high incidence of isolated lobar collapse is to be expected in tuberculosis of childhood, in which collapse is often due to pressure on an individual bronchus by an enlarged hilar gland, and in upper respiratory infections, in which aspiration collapse may well involve only one area. The explanation is not clear in asthma, where bronchial spasm is widespread and tenacious muco-pus is secreted widely through the bronchial tree. The multilobular pattern of collapse in lower respiratory infections, pertussis, sinobronchitis, and measles is to be anticipated, because in each of these conditions much muco-pus is secreted, leading to obstruction of several bronchi. Fig. 7 illustrates the high incidence of collapse of the right middle lobe in both asthma and tuberculosis, and its progressively diminishing frequency in sinobronchitis, pertussis, upper respiratory infections, measles, pneumonia, and lower respiratory infections, whereas the incidence of left lower lobe collapse shows an opposite pattern. This suggests that the pathogenesis

of the collapse in these two lobes is different, the left-lower-lobe bronchus being obstructed by aspirated or secreted muco-pus, and the right-middle-lobe bronchus becoming occluded by enlarged hilar glands with or without erosion.

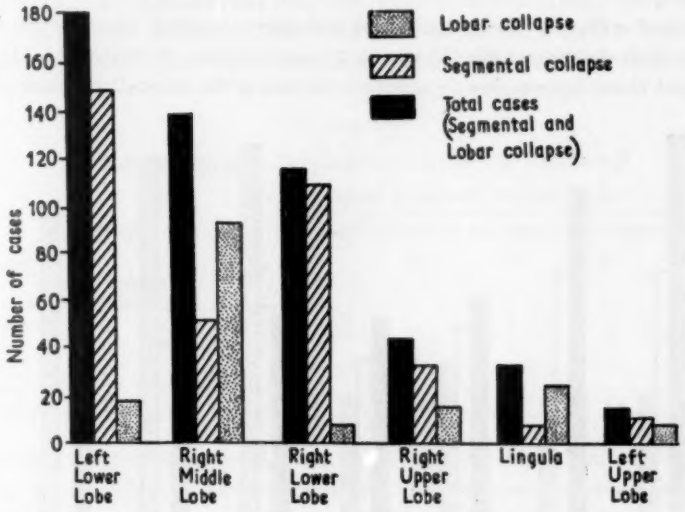

FIG. 5. Isolated lobar collapse. Comparative frequency of total lobar and segmental collapse when only a single lobe was involved.

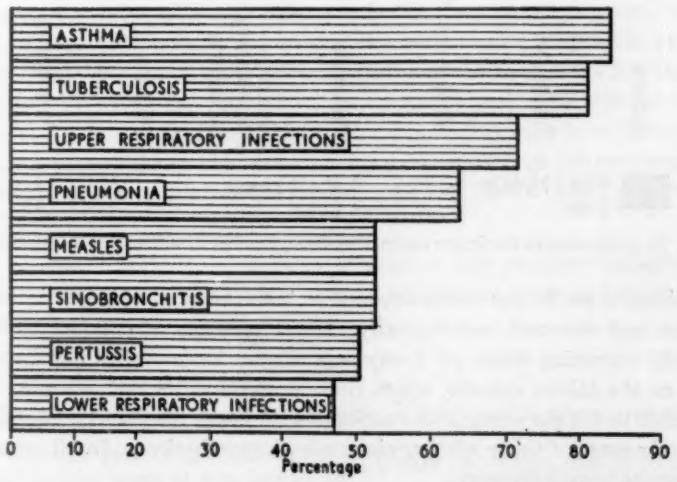

FIG. 6. Percentage of children with isolated lobar collapse.

The marked tendency of asthma to give rise to isolated collapse of the right middle lobe is, however, not easily explained. The factors causing collapse of the right middle and left lower lobe respectively may be combined in collapse of the

right lower lobe, as it occupies an intermediate position in frequency in the various aetiological groups.

Prognosis

Recurrent collapse. Recurrences of collapse occurred most often in the children with sinobronchitis (25 per cent.) and asthma (25 per cent.). It is unlikely that these figures give an accurate picture of the relapsing nature of these

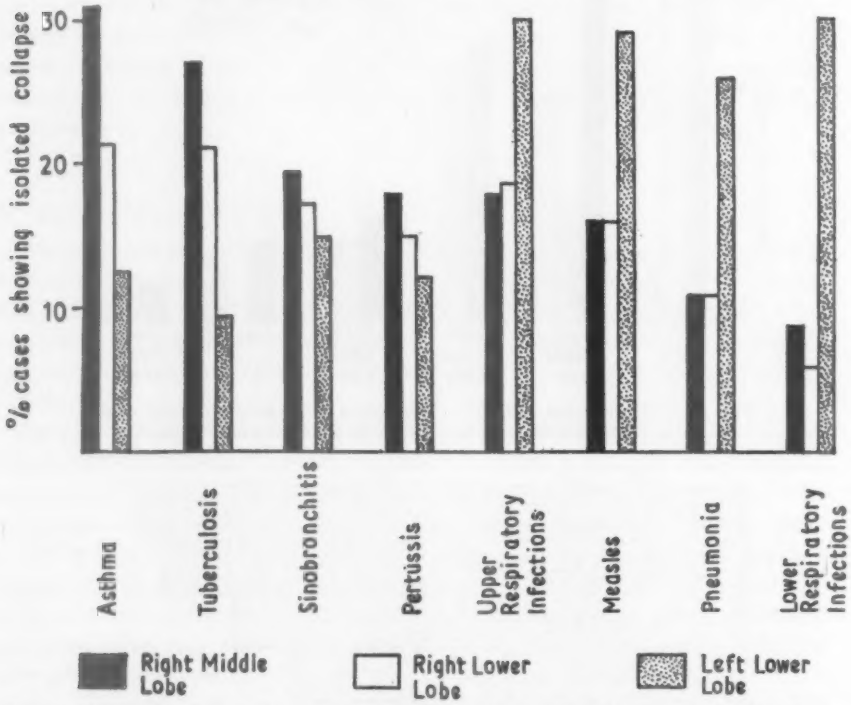

FIG. 7. To demonstrate the importance of aetiology in the distribution of isolated collapse.

conditions, since in our series account is taken only of episodes in which the collapse was detected radiologically. Other episodes of collapse were almost certainly occurring when no X-ray was taken. Recurrences due to the same cause as the initial episode, apart from sinobronchitis and asthma, were encountered in 6·9 per cent. of the patients with lower respiratory infections, and in 7·8 per cent. of those with upper respiratory infections. In all other groups recurrences were infrequent.

The duration of collapse was less than three months in 240 (57 per cent.) of 422 patients seen at the follow-up clinic (the 50 patients with persistent collapse are discussed separately). Long periods of collapse were seen particularly in sinobronchitis, pertussis, asthma, and tuberculosis. In 14 cases (3 per cent.) re-expansion was seen after an interval of one to two years (sinobronchitis

in three, upper respiratory infection in one, pertussis in five, asthma in one, and tuberculosis in four cases), but in only three cases (0·6 per cent.) did re-expansion take place after two years. One child, with lower respiratory infection and accompanying collapse, was followed up for over five years, and finally the lung re-expanded. Another child, with sinobronchitis, was followed up for three years, during which time the collapse remained unaltered, and was seen

TABLE IV

Persistent Collapse: Aetiology and Length of Follow-up

Aetiology	*Number of patients followed up for*				*Total*
	2–3 years	*3–4 years*	*4–5 years*	*over 5 years*	
Sinobronchitis	6	3	3	4	16
Lower respiratory infections	2	1	..	..	3
Upper respiratory infections	4	..	..	..	4
Pneumonia	1	..	1	1	3
Pertussis	2	..	1	2	5
Measles	..	1	..	1	2
Asthma	2	..	1	..	3
Tuberculosis	6	5	1	2	14

again after a further three years, when the X-ray was clear. The third child had collapse associated with asthma, and her lung re-expanded after more than three years.

Persistent collapse. Fifty patients (10·6 per cent.) of the 472 who attended the follow-up clinic were found to have persistent collapse, the most frequent causes being sinobronchitis and tuberculosis. It must be emphasized that the duration of persistent collapse recorded in this series depends upon the period of follow-up available in each case, but in no instance was this period less than two years. Table IV shows the number of patients with persistent collapse in each aetiological group, and the length of time for which they have been followed up. It is of value to consider the incidence of this residual damage not only according to aetiology, but also in relation to age at the onset of the collapse. This relationship is as follows:

Age	*Number of children with persistent collapse*
Under one year	3 (2·8 per cent. of children in same age group)
One to two years	7 (6·6 per cent. ,, ,, ,,)
Two to five years	15 (5 per cent. ,, ,, ,,)
Over five years	25 (7·4 per cent. ,, ,, ,,).

This means that in our series of cases the risk of persistent collapse was:

Under one year of age, one in 35
One to two years of age, one in 15 } Under two years, one in 21·2.

Two to five years of age, one in 20
Over five years of age, one in 13·5 } Over two years, one in 16.

Pulmonary collapse in young children is often attributed to their particular susceptibility to infections, and to the smallness of the bronchi, which readily become obstructed with viscid secretion. Our figures, however, show that the

risk of residual damage is less in the children under two years of age, and this difference appears to be due to difference in the aetiology of collapse at various age periods (Fig. 8). The persistent-collapse rate for the individual lobes, regardless of aetiological factors, shows that the lingular and upper lobes, which were least often involved, have been most often permanently damaged, whereas

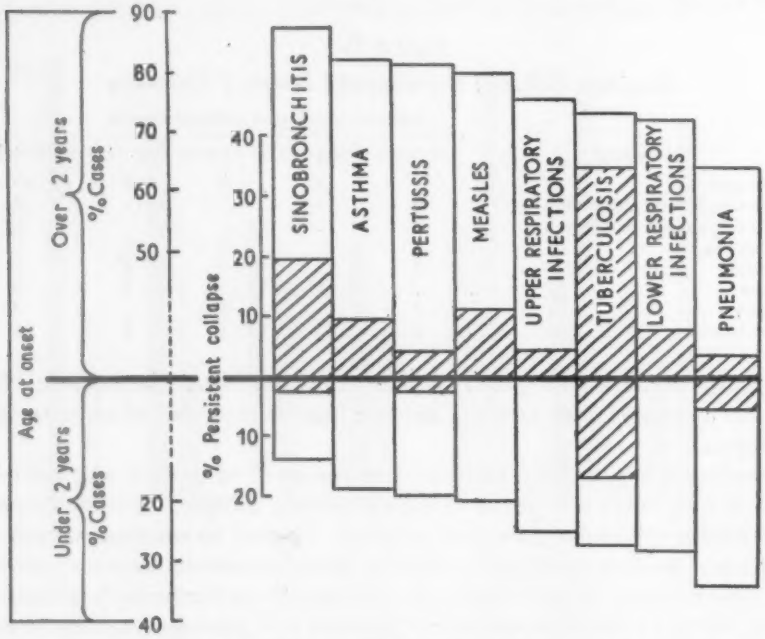

FIG. 8. Relationship between age incidence and persistence of collapse in the different aetiological groups.

White areas show percentage incidence of collapse over and under two years of age; hatched areas show the percentage of persistent collapse.

the lower lobes, which were most frequently involved, have seldom shown persistent collapse:

	Incidence of collapse (472 cases)	*Persistent collapse* (%)
Lingular lobe	92	15·2
Right upper lobe	55	12·7
Left upper lobe	16	12·5
Right middle lobe	180	10·6
Right lower lobe	155	6·4
Left lower lobe	204	6·3

Bronchiectasis. Bronchographic study in our series is at present incomplete, and no conclusions can be drawn. Of the 50 children with persistent collapse,

24 have been so examined, and eight have been shown to have definite bronchiectasis:

	Persistent collapse	*Bronchography*	*Bronchiectasis*
Sinobronchitis . . .	16	8	3
Lower respiratory infections .	3	3	0
Upper respiratory infections .	4	0	0
Pneumonia	3	2	0
Pertussis	5	4	2
Measles.	2	2	2
Asthma	3	3	0
Tuberculosis	14	2	1

Although the total incidence of bronchiectasis in our follow-up survey (1·7 per cent.) may well be lower than the true figure, it shows, with the persistent-collapse rate of 10·6 per cent., a remarkable contrast to Field's (1949) series. Of her 272 patients with pulmonary collapse 42 per cent. were found to have bronchiectasis; it may be that her cases were selected. Ours were consecutive cases of children attending any department of the hospital, and would therefore provide a wider range than those referred specially to a medical clinic on account of respiratory symptoms.

Height and weight. Variations in height and weight of the children under review did not appear to depart significantly from the normal range.

Treatment. We have not been able to correlate the effects of treatment with the progress of collapse in the present survey, on account of changing methods and the number of physicians concerned. The results of bronchoscopy, though inadequate for any definite conclusions, are in accordance with the view of Gordon (1946) and others, who have found that this procedure is of little value except when done early in children who have undergone operation and after inhalation of a foreign body.

It is a pleasure to record our thanks to our colleagues at the Princess Louise (Kensington) Hospital for Children (St. Mary's Hospital Paediatric Unit), for allowing us access to their cases, to Miss Sturgess and Miss Clouston for clerical assistance, and to Miss G. A. Kelly, who was responsible for the radiography. We are also indebted to St. Mary's Hospital Endowment Fund for help with clerical expenses.

Summary

1. A survey has been made of 854 consecutive cases of pulmonary collapse, which have been analysed in 10 groups according to aetiology.

2. The lobar pattern of collapse, the duration, and the recurrences have been contrasted in the different aetiological groups. Several lobes tended to be involved in measles, sinobronchitis, pertussis, and lower respiratory infections, whereas in asthma, tuberculosis, and upper respiratory infections isolated lobar collapse was more usual. There was no essential difference in the lobar pattern between aspiration collapse and that due to conditions in which tenacious mucus was secreted widely throughout the bronchial tree. Hilar

lymphadenopathy most often gave rise to collapse of the right middle and upper lobes. Explanation cannot be given for the high incidence of collapse of the right middle lobe in asthma and sinobronchitis.

3. No case of the 'middle lobe syndrome' was seen in the entire series.

4. Discussion of prognosis is based on the fate of 472 of the children who attended the survey follow-up clinic.

(1) Recurrence of collapse was most common in sinobronchitis and asthma.

(2) The duration of collapse was less than three months in the majority of cases, but persisted for considerably longer periods, particularly in tuberculosis, sinobronchitis, and pertussis. Re-expansion occurred in 14 patients after an interval of one to two years, and in three patients after an interval of three to six years.

(3) Collapse was still present in 10·6 per cent. of our cases after a follow-up of two years or longer. Bronchography was carried out in 24 cases, bronchiectasis being shown in eight (1·7 per cent.), but, since bronchographic study was incomplete in the whole series, the true incidence of bronchiectasis may be somewhat higher. Persistent collapse was most often seen in tuberculosis, sinobronchitis, and measles (widespread bronchiectasis was demonstrated in both children who had had measles). The lingular and upper lobes were least often affected, and yet showed a higher rate of persistent collapse than the other lobes.

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RESPIRATORY FUNCTION IN EMPHYSEMA IN RELATION TO PROGNOSIS[1]

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In the past few years many articles have appeared on the changes in pulmonary function that are found in chronic emphysema. Most of these have been concerned with the abnormalities of function found in patients with established emphysema compared with normal subjects (Baldwin, Cournand, and Richards, 1949), and few of them have dealt with the sequence of functional change as the disease progresses. Any study of a group of patients with emphysema over a period of years is faced with a number of problems, none of which can be solved entirely satisfactorily. One of these is the problem of selection of cases. Emphysema cannot be precisely defined clinically, radiological assessment is unsatisfactory, and to define emphysema in terms of function tests might well be considered premature. If, on the other hand, a rigorous clinical definition of emphysema is adopted, the cases selected will inevitably tend to be severe and advanced. The purpose of the present investigation was to select a group of patients, diagnosed according to the criteria set out below, and to follow this group over a period of years both from the clinical and from the functional viewpoint. The results so obtained have been analysed with particular problems in mind, which may be summarized as follows:

1. To confirm or disprove the accuracy of the clinical selection by careful follow-up and post-mortem analysis.
2. To determine the prognosis in emphysema uncomplicated by heart failure.
3. To relate the clinical course of the disease to changes in the function tests.

The answers that have been obtained to some of these questions are suggestive rather than final or definite, but many of the results should be of assistance in planning future studies of this kind on patients with chronic respiratory disorders.

Clinical Investigation

Selection of cases. The criteria adopted in the selection of cases of emphysema to be included in this study were as follows:

1. A history of increasing dyspnoea on exertion, constantly present in both winter and summer.
2. No other apparent cause for dyspnoea. Subjects with a blood-pressure over 140/90 were excluded.[2]

[1] Received September 9, 1955

[2] The combination of systemic hypertension and established emphysema is, in our experience, not a common one.

3. A history of chronic bronchitis, though not an essential requirement, was in fact present in all but two cases.
4. No patient was selected in whom there was clinical evidence of cor pulmonale when first seen.
5. Rejection of the subject if he appeared to be an unreliable witness (two cases), or if there were other symptoms not related to the emphysema and thought to suggest the presence of a 'functional overlay' (one case).

Eighty-eight cases of emphysema fully satisfied the criteria for inclusion set out above, but 29 of these patients have not been included in the follow-up study because they attended infrequently. The present study therefore includes 59 patients, all of whom were treated with the usual variety of antispasmodic drugs at the discretion of the physician. Many had courses of instruction in breathing exercises. The initial assessment of physical signs, and the follow-up attendance, with the assessment of dyspnoea and bronchospasm, were done by one physician (J. M. S. K.), except for short periods of absence. The physician was not informed of changes in the results of the function tests. All but one of the patients

TABLE I

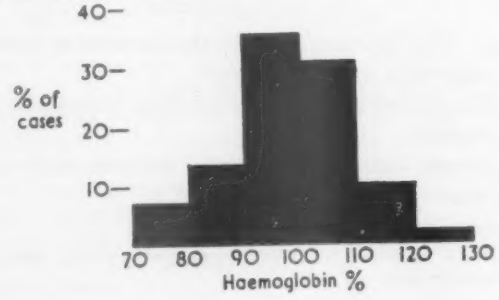
Characteristics of Patients on First Examination

Age: Mean, 57·5 years; range, 32–78 years.
Sex: Male, 57; female, 2.

	Number	%
Occupation: Labouring	7	12
Manual	33	56
Clerical	19	32
Hernia	6	10
Cyanosis*	26*	44*
Barrel-shaped chest	38	64
Area of cardiac dulness: Normal	1	2
Reduced	14	24
Absent	44	74
Percussion note: Normal	37	62
Over-resonant	22	38
Rhonchi present	25	42
Prolonged expiration	37	62
Râles present	42	71
Jugular venous pressure raised	2	4
Ankle œdema present	0	0

* Oximeter readings showed a saturation of less than 92 per cent. in only one out of 20 of these patients.

Distribution of haemoglobin values:



included in this series lived in London within a 15-mile radius of the hospital. Another group of 14 cases of 'chronic bronchitis' have been included in the present study for comparison with the main group of cases of emphysema. The criterion for the selection of this group was a definite history of recurrent winter bronchitis, without constant dyspnoea on exertion.

The assessment of physical signs. There has recently been a growing awareness of the errors involved in the assessment of physical signs, and of the wide variation customarily found between different observers. Such considerations have quite properly led to scepticism about the value of such observations, but have not produced many suggestions for any practicable alternative. Table I presents some of the characteristics of this group of 59 cases of emphysema. It is generally recognized that the careful assessment of dyspnoea, by questioning and observation over a period, is more valuable in the diagnosis of emphysema than the presence of any of the individual physical signs of the condition, many of which are found in normal people of the same age group (Christie, 1944). Two points in this table call for comment. The first is that, although the observer noted 'cyanosis' in 26 cases, subsequent measurement of the arterial oxygen saturation in 20 of these patients revealed an arterial saturation below 92 per cent. in only one case. This indicates either that most of the patients had peripheral cyanosis, or that the clinical recognition of cyanosis is inaccurate. The work by Comroe and Botelho (1947) on the disparity between observed cyanosis and measured arterial saturation would support either of these conclusions. The second point is the general absence of polycythaemia in these patients—a finding which we suspect to be at variance with clinical experience in other countries. A further point of interest is the relatively small number of patients whose occupation had involved hard physical labour, many of the patients having had sedentary clerical work all their lives.

Criteria of dyspnoea and spasm. The degree of dyspnoea was graded by the physician according to the following scale of assessment:

Grade 0. Patient's performance normal for a man of his age.

Grade 1. *Patient capable of light work.* He can walk up to one mile on the level, and can climb a dozen stairs without undue distress.

Grade 2. *Patient capable of sedentary work.* He can get to and from his place of work; that is, he can walk up to 500 yards on the level without stopping. He can carry out purely sedentary work, and can assist in light household duties.

Grade 3. *Patient capable of no work.* He can move about the house, but is unable to get to and from his place of work. He can assist only in very light household duties, such as laying the table.

Grade 4. Dyspnoea on some days grade 5, on other days grade 3.

Grade 5. Patient bed-ridden; unable to move without dyspnoea.

The degree of bronchospasm was graded as follows:

Grade 0. No evidence of spasm; no rhonchi.

Grade 1. Slight spasm; occasional rhonchus.
Grade 2. Moderate diffuse spasm; rhonchi over most of the chest.

One experiment to estimate 'observer error' (Fletcher, 1952) suggested that fair agreement might be expected between observers in deciding whether rhonchi were present or not. Twenty patients were examined. Eight independent observers agreed on the presence or absence of rhonchi in 10 of them, seven were in agreement in a further two, and six were in agreement in a further six

TABLE II

Deaths

Number of patients in the series	59
Cause of death:	
Unknown	1
Carcinoma of bronchus	1
In hospital: cor pulmonale (confirmed post-mortem)	7
In hospital: cor pulmonale (no post-mortem examination)	1
At home: certified by doctor as heart failure and pneumonia	5
In hospital: other causes, but emphysema confirmed post-mortem (one from haematemesis; one after partial gastrectomy)	2

Probable incidence of cor pulmonale: 13 (or 76 per cent. of all deaths).

cases. Considering the probable variability in the presence or absence of the sign in some of the patients, this score represented a fair measure of agreement.

Frequency of follow-up visits. As has been stated already, patients who could not attend regularly have not been included in the survey. With one or two exceptions, all those included were seen at least every two months. The average period of observation was three years, and with the exception of some patients who died, none was observed for less than two years. Details of attendance for function testing are given in a later section.

Fatal cases. Table II shows the number of patients included in the series who died. It will be seen that the presence of emphysema was confirmed in all those in whom post-mortem examinations were obtained. Three-quarters of the patients who died have shown evidence of right heart failure. From the tables of life expectation it can be calculated that four deaths would be predicted in this group of subjects in a three-year period, and this figure may be compared to the 13 respiratory deaths, and four deaths from other causes, which occurred.

Relationship of the degree of disability to the season of the year. Fig. 1 shows the relationship between the mean level of dyspnoea and the season of the year. Only those patients are included who were seen and assessed several times during the period concerned. Since new cases were being added to the series throughout the five-year period, comparisons are only possible between the average grade of dyspnoea in the same patient during successive seasons. This figure confirms the clinical impression of worsening of dyspnoea during the winter months. In addition it shows that a peak of disability was reached during the winter of 1952–3, at the time of the severe fog which occurred in December 1952 (Report No. 95, 1954). Three patients in this group died at the time of this fog, and the complaint of increased disability following it was general.

Relationship between the prevalence of rhonchi and the season. Fig. 2 is plotted in a similar manner to Fig. 1. Although some improvement is recorded on the

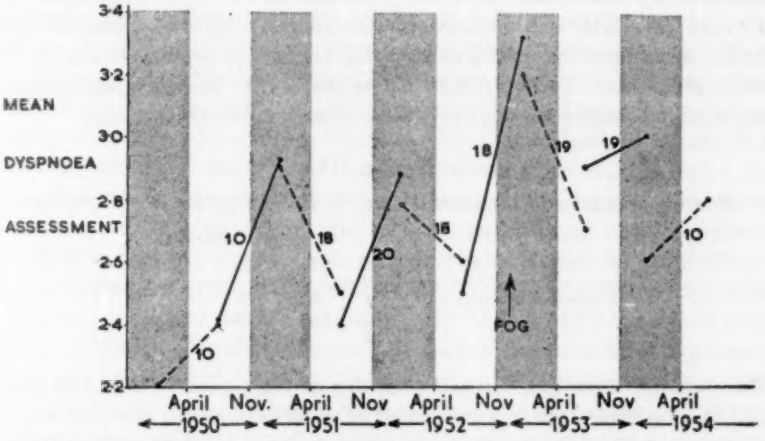


FIG. 1. Relationship between dyspnoea and season of the year. The ordinate is the mean grade of dyspnoea (see text for details of classification). The lines connect observations made on the same group of patients: broken lines, winter to following summer; continuous lines, summer to following winter. The figures indicate the number of patients in each group. Note the almost uniform deterioration in winter, and the apparent peak of disability in the winter of 1952–3.

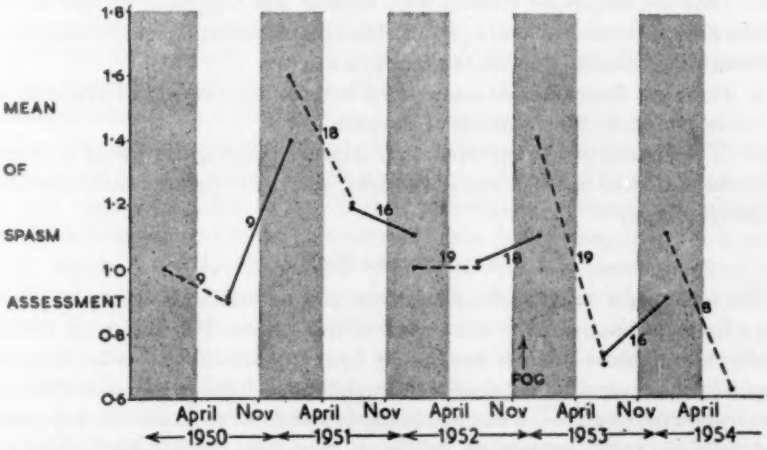


FIG. 2. Relationship between bronchospasm and season. Lines and figures as in Fig. 1. The ordinate is the mean assessment of degree of bronchospasm (see text for details of classification). Apart from a usual improvement in summer compared with the preceding winter, there is little uniform change. There is no peak in the winter of 1952–3.

average during the summer, the relationship to season is less pronounced than in the case of dyspnoea. In particular there is no obvious change in the winter of 1952–3. These observations are not suitable for any more precise analysis,

as the inaccuracy introduced by 'observer error' and by daily variation must be very considerable.

Relationship between the prevalence of rhonchi and the degree of dyspnoea. Table III shows the relationship between the assessment of dyspnoea and the rhonchi noted in these subjects. It will be seen that there is no close agreement between these observations. The most that can be said is that there is a bias toward the more disabled subject having the greater clinical evidence of spasm.

TABLE III

Relationship between Assessed Degree of Bronchospasm and Dyspnoea

		Grade of Dyspnoea				
		1	*2*	*3*	*4*	*5*
Degree of spasm:	0	4	15	10	1	0
	1	0	18	16	7	2
	2	2	9	21	9	2

Conclusions. 1. During the course of this investigation 17 of the 59 patients died. Taking their ages and the period of observation into account, only four should have died, if their expectation of life had been as indicated in the insurance tables.

2. Although none of the 59 patients showed evidence of heart failure when first seen, eight, or 13 per cent., died with pulmonary heart failure within two years, and 13, or 22 per cent., within four years.

3. That the diagnostic criteria were reliable was suggested by the fact that all the nine patients on whom a post-mortem examination was performed showed histological evidence of advanced emphysema.

4. There is a demonstrable seasonal variation in the severity of dyspnoea and, to a less extent, in the incidence of rhonchi.

5. Of the patients who survived, four improved during the period of observation, the condition of seven was unchanged, and the remainder showed evidence of deterioration.

Function Tests

The techniques used for the assessment of function in this group of patients have been unchanged over the period of five years. The timing of the tests made on individual subjects has mostly been haphazard, but as far as possible they have been equally distributed throughout the different seasons of the year. The results obtained when the whole battery of function tests was repeated on alternate days on one subject, while an in-patient, shows little day-to-day variation (see Fig. 7). It is to be expected, however, that the week-to-week variations on out-patients may on occasions be considerable, especially during the winter months.

Methods. 1. *Subdivisions of lung volume and mixing efficiency.* The circuit used for these measurements has been described in detail previously (Bates and Christie, 1950). Consecutive estimates of the functional residual capacity in normal subjects with this technique showed that the standard deviation of the

differences between duplicate estimates is ±65 ml. (Bates, 1954). The method used to calculate the mixing efficiency has the merit of being simple, and of being more or less independent of tidal volume and lung volume. Experiments subsequent to the original description (Bates, 1954) have shown that the index is sensitive to the respiratory rate, though this effect is not serious except at extreme ranges. Recently there have been attempts to analyse the nature of the mixing defect in patients with emphysema by calculation of the apparent volume of a poorly ventilated space within the lung (Prime and Westlake, 1954; Blair and Hickam, 1955). However, a comparison between cases of emphysema and normal subjects breathing at a raised respiratory level has suggested that such calculations have little functional and still less pathological meaning (Bates, Fowler, Forster, and van Lingen, 1954), and their value is doubtful. Immediately consecutive estimates of the mixing efficiency (per cent.) in 20 cases of emphysema showed a standard deviation of only ±2·6 (Bates, 1954), but the known sensitivity of the index to bronchospasm means that a considerable day-to-day variation may be expected in any condition in which bronchospasm plays a part.

2. *Maximal ventilatory volume.* Although the maximal ventilatory volume has been measured several times in most of the patients in this series, these figures have only been used in assessing the progress of individual patients. The maximal ventilatory volume exceeded 40 litres per minute in few of the patients, and in the majority it was 30 litres per minute or less. With this severe degree of disability the sensitivity of the test in detecting change was clearly slight. The results obtained in a few cases are, however, mentioned later. The technique followed has been that used by Wright (1950), with a low-resistance valve box and two Douglas bags. Details of this circuit and its performance have been recorded elsewhere (Bates, 1954).

3. *Measurement of the diffusing capacity.* Riley, and those who have worked with him, have given much attention to the problem of measuring the diffusing capacity of the lung in patients with respiratory disorder (Donald, Renzetti, Riley, and Cournand, 1952; Cohn, Carroll, Armstrong, Shepard, and Riley, 1954). This measurement is the quantity of a gas, such as oxygen, which can pass per minute from the alveoli into the blood with a pressure gradient of 1 mm. Hg. In general terms, it is a measure of the ability of the lungs to aerate the blood. For various reasons it is easier to measure the diffusing capacity of carbon monoxide than of oxygen, and since these two gases are believed to behave similarly, the diffusing capacity of the lungs for carbon monoxide has the same functional significance as that for oxygen. The technique used in making this measurement has been described elsewhere (Bates, 1952). An approximate indication of the diffusing capacity was initially obtained by measurement of the percentage uptake of carbon monoxide during continuous breathing, although it was recognized that the dependence of the percentage uptake of the gas on the minute-volume respired detracted from its value as an index of derangement of function. The only way of eliminating this effect of changing minute-volumes is to calculate the diffusing capacity (D_{CO}) as an index of the rate of uptake of the gas per minute per mm. Hg pressure-gradient

between the gas and the blood. If the 'back pressure' of carbon monoxide in the blood is ignored, as in most cases it can safely be, the diffusing capacity can be calculated by dividing the rate of uptake of carbon monoxide by the mean alveolar tension of carbon monoxide. In a recent communication (Bates, Boucot, and Dormer, 1955) this technique has been studied in detail in normal subjects at rest and on exercise. If the mean alveolar carbon monoxide is calculated from the Bohr equation, using an assumed value for the respiratory dead space, the resulting estimate of D_{CO} will occasionally be too high, especially if the tidal volume is small. One may expect, therefore, that the values of D_{CO} in the present study will tend to be falsely high, or in the case of emphysema more nearly normal, as a result of this effect. The problem of the precise validity of any method of calculating a mean alveolar carbon-monoxide tension in emphysema will be discussed in detail elsewhere, but the present technique has the advantage of simplicity; its precision may well be improved as a result of further work. All the estimates of D_{CO} in this series have been made with the subjects at rest, except those illustrated in Fig. 5.

4. *Oxygen saturation* was measured in a number of subjects by the use of an ear oximeter. The calibration of this apparatus had been checked on five occasions down to 70 per cent. oxyhaemoglobin, against the oxygen saturation of an arterial blood sample withdrawn while the oximeter was being used, and the maximum deviation was 4 per cent. The resting oxygen saturation was below 92 per cent. in only two subjects out of 20 in this series who have been studied. It is clear that this measurement is too insensitive a test of function at rest, and that either the arterial oxygen tension must be measured or the saturation must be studied during exercise; neither of these estimations has been done.

Results of function tests. Table IV enumerates the tests of function performed. All the results obtained from every subject in this series have been included in the analysis, except eight consecutive estimates of diffusing capacity (D_{CO}) in which there was reason to suppose that there was an error in gas analysis. On an average, four sets of the ventilatory tests have been done on each subject, and the average interval between the first and last tests on each subject was two and a half years.

The relationship of these tests to the severity of the disease is shown in Fig. 3. To avoid biasing the results by frequent repetition of similar findings in one subject, only two series of function tests at the same grade of dyspnoea have been included for any one subject. In this figure are shown also the results in the small group of patients considered to have chronic bronchitis. The 'poor prognosis' group of cases of emphysema comprises those patients who died of emphysema within six months of the last function test. It will be seen that this figure, if read from left to right, represents progressive severity of the disease, as far as that can be assessed clinically. It is apparent that, although the mean results are changing in the expected direction from left to right, there is very considerable overlap between all the groups in most of the tests. Only the test of diffusing capacity (D_{CO}) achieved complete separation between the 'chronic

bronchitis' and 'poor prognosis' groups. The high upper limit of D_{CO} in the dyspnoea grades 2 and 3 is accounted for by the results in two patients, who are discussed in detail below. This figure suggests that there is general agreement

TABLE IV

Function Tests Performed

Number of patients	59
Number of estimates of: vital capacity	221
functional residual capacity	221
mixing efficiency	221
diffusing capacity (D_{CO})	153

Average interval between first and last tests on individual subjects: 2·5 years.

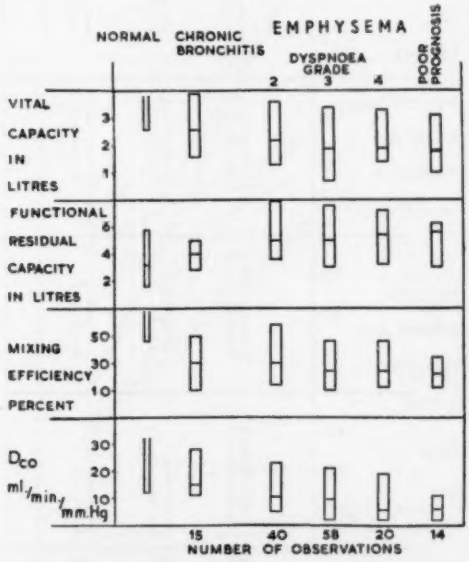


FIG. 3. Relationship between function tests and stage or severity of disease. The rectangles indicate range and mean. See text for classification of grades of dyspnoea within the emphysema group. The 'poor prognosis' group consists of patients with emphysema who died within six months of the last function test. There is a general deterioration in the means of the results from left to right—that is, as severity increases. Note that there is no overlap between the chronic bronchitis and 'poor prognosis' groups in the tests of diffusing capacity (D_{CO}), whereas there is considerable overlap in all the other tests. See text for comment on the high values for D_{CO} and mixing efficiency recorded from some patients.

between the severity of the disease as assessed clinically and the tests of respiratory function, the closest agreement being with the diffusing capacity (D_{CO}). A similar analysis of the results of function tests in relation to the degree of

bronchospasm as assessed clinically is shown in Fig. 4. Although some degree of correlation might be claimed, it is not impressive. Figs. 3 and 4 are open to the objection that the discriminating value of these tests might be obscured when the results of many tests on a considerable number of patients are considered together. Thus although, for instance, the correlation of a particular value in any one test with a particular degree of dyspnoea may be poor when

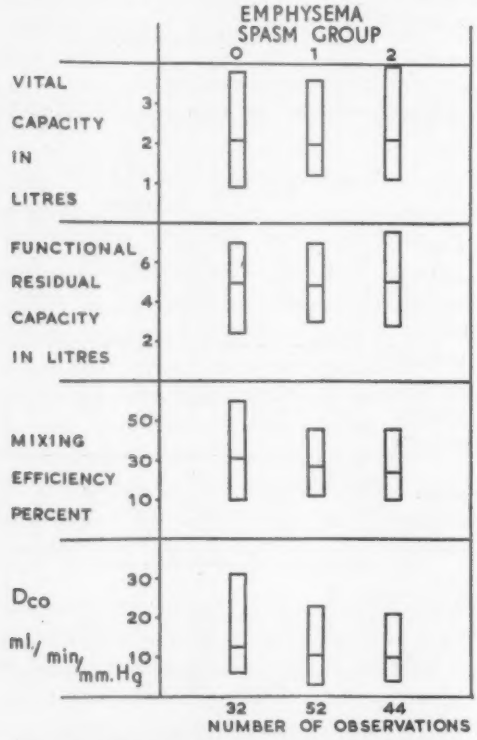


FIG. 4. Relationship between degree of bronchospasm and function tests. The rectangles indicate range and mean. Apart from a slight progressive deterioration in the mixing efficiency, the results of the function tests do not correlate with the degree of bronchospasm as assessed clinically.

numbers of patients are considered together, yet the tests may reflect increasing disability in any one patient. For this reason it may be said that certain tests, which are of little value in diagnosis, may be useful in following progress in individual cases. This possibility could clearly be investigated by comparing any change in the degree of dyspnoea or spasm with the changes in the tests of function. Unfortunately this is not possible, since in many instances the clinical assessment was not done at the same time as the respiratory function tests, and it is well known that the day-to-day variation of dyspnoea in this disease may be considerable. Fig. 5 shows the effect of exercise on the diffusing capacity of

normal subjects and patients with emphysema, and it is clear that a much greater degree of discrimination is achieved if the patients are studied on exercise. The normal individual on exercise will usually nearly double the diffusing capacity, but this increase is lost in emphysema.

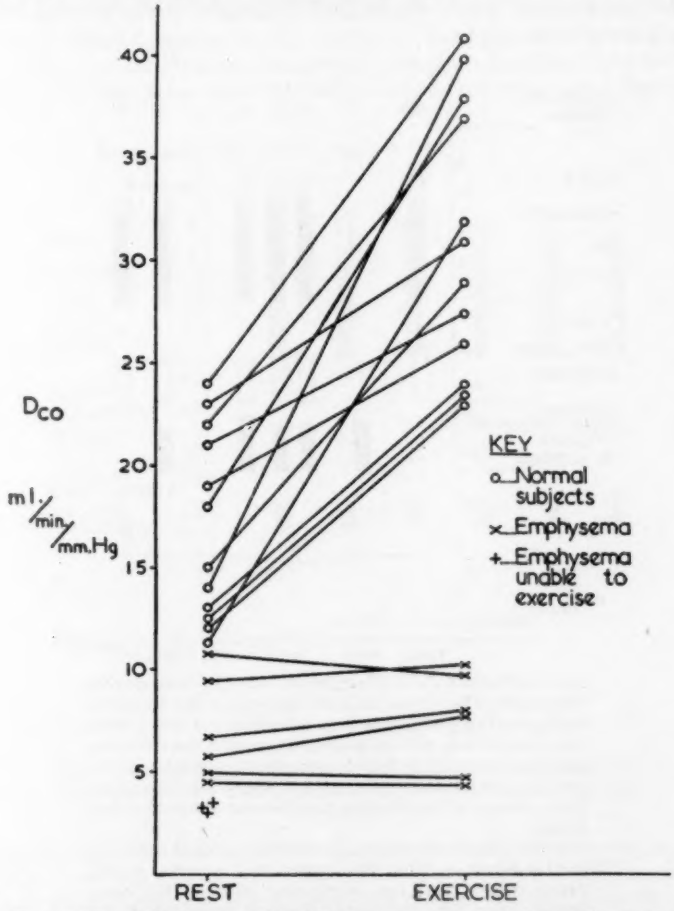


FIG. 5. The diffusing capacity (D_{CO}) on exercise. The figure illustrates the much greater discrimination between normal persons and patients with emphysema when the diffusing capacity is measured during exercise. Exercise consisted of walking at two to three miles per hour on the level.

Discussion of Individual Cases

Tests of function may be of clinical value either if they are sufficiently discriminating to be useful in diagnosis, or if they are sufficiently accurate and consistent to be useful in prognosis. There can be no doubt of the value of these tests in diagnosis. To assess their value in prognosis it is necessary to determine the consistency of their results in individual patients and, if this is

sufficiently accurate, to follow up a number of patients for a sufficient length of time to determine the relationship of changes in function to prognosis. The consistency of these tests as shown in Fig. 7 is clearly good. The relationship of function to clinical progress has been determined in all of the 59 patients of the series, and, as the results can only be given in graphic form, it is only possible to discuss illustrative examples.

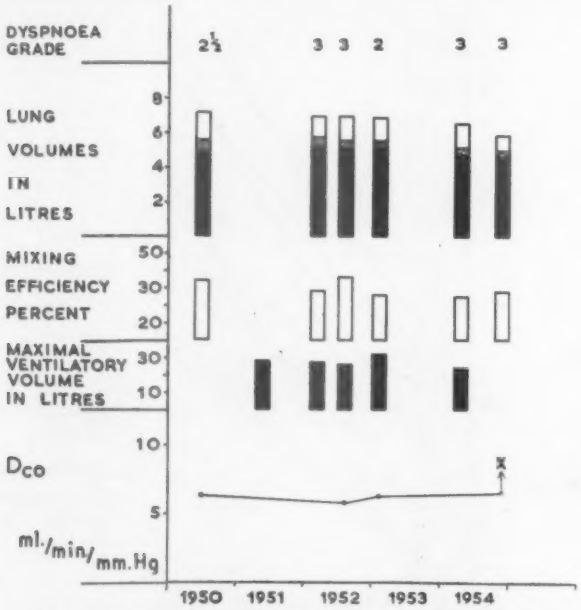


FIG. 6. Patient J. D. Changes in function tests during five years. The physician's assessment of the degree of dyspnoea is given at the top. At the end of this period the patient was still capable of increasing the diffusing capacity from 6·3 to 8·3 ml. per minute per mm. Hg on exercise, as shown by the arrow. There has been very little change in the clinical condition or in the function tests.

In this and subsequent figures the residual capacity is the black section, the expiratory reserve is the hatched area, and the inspiratory capacity the open space. Thus the functional residual capacity is the hatched and black rectangles, and the vital capacity the hatched and clear areas.

1. *Cases showing remarkable constancy.* From a number of these patients in whom very little change has occurred during the years of observation, one may be selected for illustrative purposes.

Patient J. D. was 52 years old when first seen in July 1950. He had been employed in a clerical capacity on the Stock Exchange for many years. He gave a history of a chronic winter cough for 10 years, productive of very little sputum, and had noticed progressive dyspnoea for the last two years. When first seen he could manage one flight of stairs, but no more. He had noticed that his chest was more wheezy, and his dyspnoea worse, in foggy weather. Clinical examina-

tion revealed a barrel-shaped chest, with a moderate dorsal kyphosis. The area of cardiac dullness was absent. Initially no rhonchi were heard, though bronchospasm was noted to be present on a visit a few months later, and on most of the many occasions on which he was seen during the next five years. His subsequent progress is summarized in Fig. 6. During the period covered by this figure he was seen regularly every month or, occasionally, every other month. He complained of increased dyspnoea during the fog of December 1952, and an increase in the jugular venous pressure was noted after this. In April 1954 he had an acute chest infection, from which he made a satisfactory recovery. The function

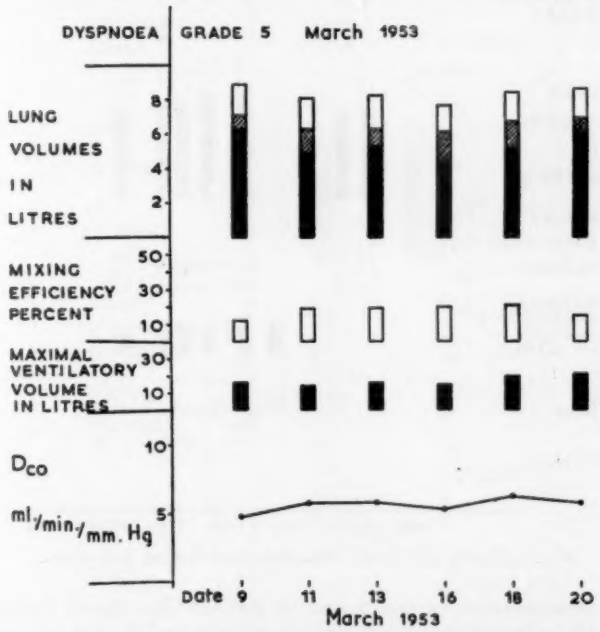


FIG. 7. Patient F. C. W. Function tests repeated every other day while the patient was in hospital. Divisions of lung volume as in Fig. 6.

tests reveal very little change during this period of supervision, and at the end of it this patient was still able to increase the D_{CO} from 6·3 to 8·3 on exercise.

2. *Cases illustrating clinical and functional change.* Patient F. C. W. was first seen in March 1950. By trade he was a meter assembler, doing a light factory-bench job. He was 32 years old when first seen, and gave a history of one year of non-productive cough, followed by rapidly increasing dyspnoea on exertion, and it was this symptom that brought him to hospital. When first seen he was just able to manage a flight of stairs. There had been no history of asthma either in the patient or in the family. He was a tall, thin man, who had evidently lost weight. An upper dorsal kyphosis was noted, and there were signs of moderate diffuse bronchospasm. The chest X-ray showed flattened diaphragms and 'some evidence of emphysema'. The patient complained of steadily increasing dyspnoea up to the spring of 1953. He was made worse by the fog of December 1952, and was admitted to hospital in March 1953 for a course of antibiotics. While he was in hospital all the function tests were repeated every other day for

10 days, and can be seen from Fig. 7 to show a satisfactory degree of consistency. Their results showed a greater degree of impairment than those obtained previously, but in the spring of 1954 the patient appeared to be better, and this change was paralleled by apparent improvement in the function tests (Fig. 8).

Patient F. M. shows a rather more rapidly progressive course. He was first seen in December 1948, when he was aged 61 years. He was a cook on a railway dining-car. He gave a one-year history of cough with sputum, and of steadily increasing dyspnoea. He said that the amount of sputum had always been

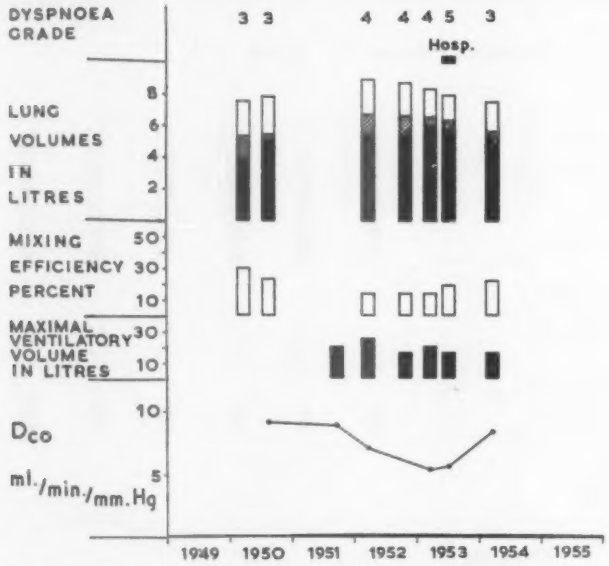


FIG. 8. Patient F. C. W. Function tests during five years.

scanty. On examination he was found to present the typical features of emphysema, with a barrel-shaped chest, poor air entry at the lung bases, and diffuse 'bronchospasm'. In March 1950 his condition was unchanged, and he was still at work. In November 1950 he had an attack of bronchitis, after which he was noticed to be more dyspnoeic. In February 1951 he was admitted to hospital with heart failure and ankle oedema. The changes in function tests are shown in Fig. 9. The heart failure responded to treatment, but recurred in June 1951. The oedema again disappeared, but in December 1951, after a slight fog, he was more breathless again, and he died in hospital with oedema and heart failure. Post-mortem the lungs showed generalized emphysema; no bullae were larger than about 1 cm. in diameter, but only a few small islands of normal alveolar tissue were present in the lungs.

Two patients showed a long period of stability followed by a fairly rapid decline. The progress of one of these is illustrated in Fig. 10. This patient (B. H.) was a clerk by occupation, and was 59 years old when first seen in October 1949. He said he had had a slight cough, never productive of much sputum, for some years. In 1942 he had won a 'doubles' tennis tournament, and had noticed no dyspnoea. Dyspnoea began in 1947, and had progressed rapidly, so that when he was first seen it was classed as grade 3. Physical signs at that time revealed a barrel-shaped chest with moderate kyphosis, reduced air entry at the bases,

and no evidence of bronchospasm. He continued with little change, except that between 1952 and 1954 he required repeated blood transfusions as treatment of an aplastic anaemia which followed a course of chloramphenicol. By 1954, however, he was maintaining a normal haemoglobin level without further transfusions. In December 1954 he was more breathless, and was unable to manage the journey to hospital. He was admitted to hospital in 1955, and was then virtually bedridden: on his best days he could manage to walk about 20 yards before having to stop. His liver was for the first time enlarged, but there was no ankle oedema. The only other change was an increased prominence of the P

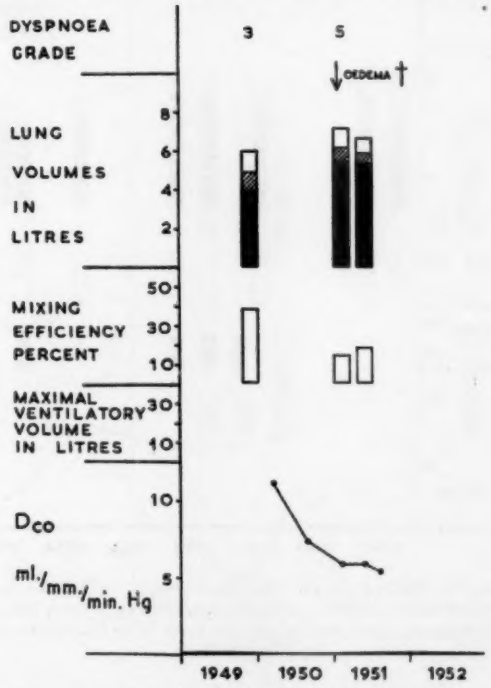


FIG. 9. Patient F. M. The relatively rapid clinical deterioration before death in December 1951 has been paralleled by adverse changes in all the function tests.

waves in Lead II of the electrocardiogram. It will be seen that this clinical deterioration was paralleled by a falling D_{CO}; changes in the ventilatory indices of function have been slight.

Only two patients showed evidence of clinical and functional improvement. One of these (W. C.) showed improvement in a fairly short period of time. He was 49 years old, and on the editorial staff of a London newspaper. He had a long history of recurrent winter bronchitis, and some catarrh. After the fog of December 1952 he became increasingly dyspnoeic, and visited the hospital on account of increasing disability in September 1953. By this time he was too breathless to work, and he was conscious of considerable wheezing in his chest. He was admitted to the ward, where he was found to have a slightly increased jugular venous pressure, but no ankle oedema. There was a considerable increase in the anteroposterior diameter of the chest, and movement was

very poor. Generalized rhonchi were heard, with a few basal râles. The electrocardiogram was normal, and the chest X-ray showed only some 'hypertranslucency'. He was treated with terramycin and antispasmodics, and his progress is shown in Fig. 11. It is of interest that the D_{CO} has risen progressively, although there has been no change in the efficiency of gas distribution. There has been a striking decrease in functional residual capacity, which is of interest in view of the general failure of this measurement to correlate with

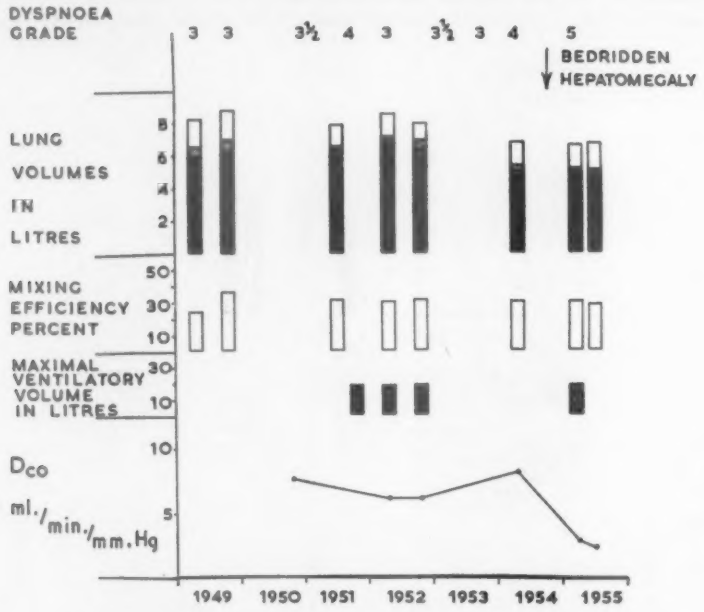


FIG. 10. Patient B. H. The onset of cor pulmonale and clinical deterioration has been paralleled only by a falling diffusing capacity, and there has been little change in the ventilatory tests.

other changes. This case illustrates the occasional finding of improvement, both clinically and by tests of function, in these patients. Possible mechanisms for these changes are discussed later.

3. *Cases probably erroneously selected.* No patient initially included in this series has been subsequently rejected, except two who developed pulmonary tuberculosis and carcinoma of the bronchus respectively. In two cases, however, it seems likely that the original selection was erroneous. These merit special discussion, because such patients may very easily be labelled 'chronic emphysema', and their inclusion in such a group may seriously influence the results obtained.

The first patient, H. W., was 43 years old when he was first seen in January 1951. He was a fireman, but had spent about five years in a coal mine in the past, ending this job when he was aged 20. He gave a four-year history of cough, predominantly in winter, and productive of very little sputum. He complained of steadily increasing dyspnoea for the last three years, together with some

wheezing in the chest. Dyspnoea was beginning to interfere with his work. On examination it was noticed that his chest was not markedly barrel-shaped, and there was moderate diffuse bronchospasm. Clinically it was thought that he had moderate emphysema, with a considerable degree of bronchospasm. The chest X-ray showed no evidence of pneumoconiosis. His progress is recorded in Table V. In May 1953 he was completely free of symptoms, and able to do gymnastics. He has had no treatment since January 1954. There can be very little doubt that this man's disability was entirely due to bronchospasm.

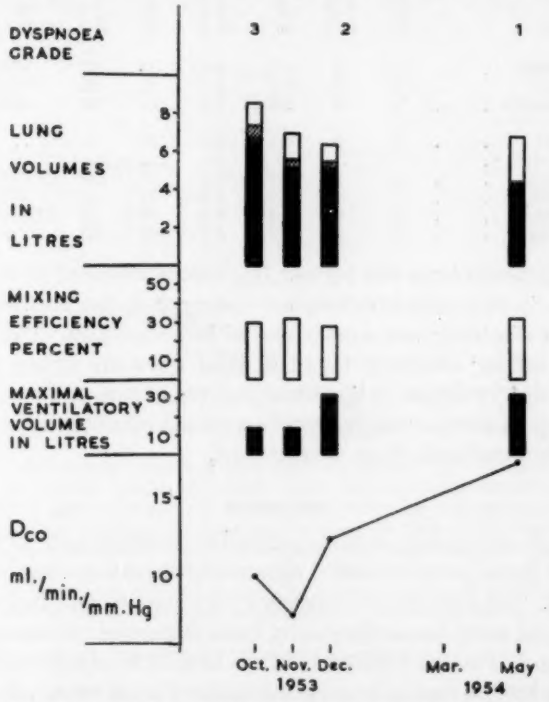


FIG. 11. Patient W. C. Note the improvement in dyspnoea and in diffusion.

The normal D_{CO} was the main pointer to this diagnosis when he was first seen. The failure of the vital capacity to reflect his improvement is very striking.

The second case of this type was G. W. This man was 45 years old when he was first seen in January 1951. By occupation he was a race-course 'tic-tac' man. He said that he had had a winter cough for as long as he could remember, usually productive of thick sputum. He could manage two to three flights of stairs, and had noticed considerable wheezing in the chest. His dyspnoea was assessed as grade 2. On examination the clinician noted 'no true barrel-chest'. The apex beat could not be located, and there was moderate diffuse bronchospasm. His progress is summarized in Table V. In this patient the physician noted, in December 1953, 'despite fog, no undue dyspnoea'. As in the previous patient, although the initial ventilatory function tests were perfectly compatible with emphysema, the D_{CO} was high. The fact that he still complained of dyspnoea in July 1953 is difficult to explain.

TABLE V

Patients probably Erroneously Selected

Patient	*Date*	*Dyspnoea (grade)*	*Bronchospasm (grade)*	*Vital capacity (litres)*	*Functional residual capacity (litres)*	*Mixing efficiency (%)*	*D_{CO} (ml./min./mm.Hg)*	*Tidal volume (ml.)*	*Maximal ventilatory volume (litres)*	*Oxyhaemoglobin (%)*
H. W.										
	March 1952	1–2	2	4·2	3·4	35	27	960	50	..
	Jan. 1953	0	0	3·8	2·9	51	21	790	90	..
	April 1954	0	0	3·5	2·4	61	31	598	..	98
G. W.										
	Jan. 1951	2	2	2·6	5·9	20	..	..	..	..
	Aug. 1951	..	..	..	..	..	..	..	22	..
	March 1952	1	2	2·7	6·5	30	19	870	..	..
	Nov. 1952	2	1	2·6	7·0	27	18	890	37	..
	July 1953	2	0	2·6	6·2	60	18	1,120	52	..
	April 1954	2	1	2·7	5·2	43	23	1,350	..	..

These two patients have the highest D_{CO} values recorded in the series, and it seems likely, in view of their subsequent history, that they both had bronchitis, and that their disability was mostly due to bronchospasm. The considerable variations in mixing efficiency found in both cases are strong confirmatory evidence for this hypothesis. It is evident that the inclusion of a number of such cases in a group labelled as 'emphysema' may much effect the apparent response of the group to a particular form of treatment.

Discussion

The present investigation contains a number of defects, some of which might, in retrospect, have been avoided; others are almost inseparable from this type of study. The difficulty of arranging both clinical and functional assessment on isolated visits has undoubtedly been responsible for some of the wide variations found. Further refinement of the tests is required, and in particular it is clear that studies during exercise would be of much more value than those done while the subject is at rest. The results of this study confirm the general view of the nature of the functional defect in emphysema, namely that there is a gross impairment of the efficiency of ventilation, and of overall diffusion, within the lung. The nature of the progression from normality to death from pulmonary heart failure is indicated in Fig. 12, which is compiled partly from figures in the present series and partly from data recorded elsewhere (Bates, 1954). There appears to be no doubt that the increasing severity of emphysema is related to progressive impairment in gas diffusion.

Shepard, Cohn, Cohen, Armstrong, Carroll, Donoso, and Riley (1955) have recently shown that, in a group of cases of chronic bronchitis and emphysema, there is often a striking disparity between the vital capacity and maximal breathing capacity on the one hand, and diffusion on the other. Our findings are in complete agreement with this conclusion, and scatter-diagrams compiled from our data show no evidence of correlation between the values in question.

The evidence in the present series of the prognostic value of the diffusing capacity (D_{CO}) indicates that this measurement, or some refinement of it, is an essential part of any complete assessment of respiratory function. It seems very probable, as Riley has suggested, that the D_{CO} in emphysema is primarily a measurement of the degree of destruction of the lung parenchyma, and presumably this

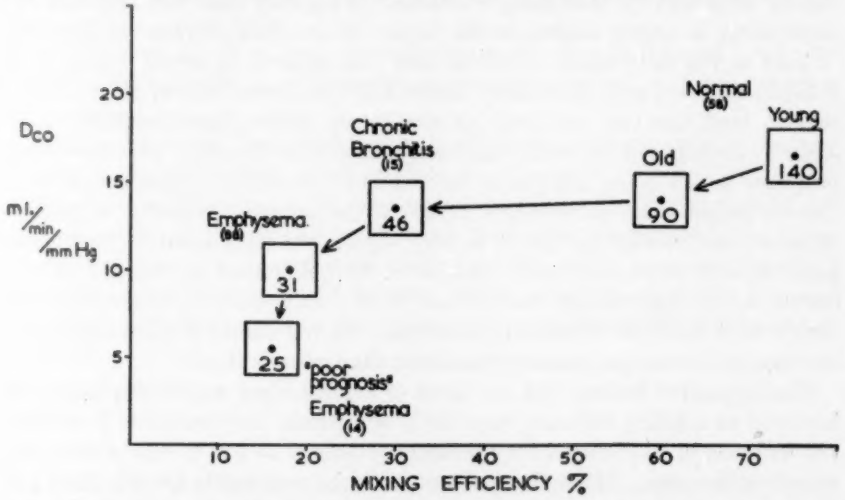


FIG. 12. The relationship of tests of function to prognosis. This figure is compiled partly from data in the present study, and partly from data recorded elsewhere (Bates, 1954). The central dot in each rectangle marks the mean value for each group, but the area enclosed by it does not represent the range of values, as there is an overlap between all successive groups. The figure in each rectangle is the mean maximal ventilatory volume for each group (maximum breathing capacity) in litres. The small figures in parentheses are the numbers of subjects in each group. The change which follows the onset of chronic bronchitis is mainly ventilatory, and is concerned with bronchial obstruction; the progression from chronic bronchitis to death in cor pulmonale is principally followed by a falling diffusing capacity. See text for criteria of classification.

accounts for its value in prognosis. Evidence will be presented elsewhere that bronchospasm alone is, in certain circumstances, capable of lowering the overall diffusing capacity, presumably by reducing the effective surface area of blood exposed to ventilating gas. For clear evidence, therefore, of improvement in gas diffusion in emphysema, it is essential that the effect of a reduction in bronchospasm can be ruled out. In the patient W. C. (pp. 151–2; Fig. 11), there was an improvement in the overall D_{CO} without any change in mixing efficiency, and although this fact suggests that the degree of bronchospasm had not altered, it is by no means conclusive. We have yet to demonstrate, by combined pressure volume and diffusion studies, that improvement in diffusion can occur without change in bronchospasm. Such an event is of course a theoretical possibility, particularly if any degree of pulmonary oedema is responsible for the lowering of D_{CO} in these subjects.

The clinical and functional findings in this group of cases have led us to certain tentative conclusions. In London, it is true that the majority of cases of

advanced emphysema have a long history of chronic bronchitis; in such patients it must be supposed that the progressive damage to the lung parenchyma (that is, emphysema) is a result of the strain of constant bronchiolar obstruction and cough in an ageing lung. A similar sequence of events may occur as a result of asthma, but in the present group of 59 cases of emphysema no patient had a history of allergy or true allergic asthma. It appears that the dyspnoea of emphysema is mainly related to the degree of bronchial obstruction present, at least in the early stages of the disease. The absence of precise correlation between diffusion and ventilatory defect has been noted above. These facts suggest that the two processes of ventilatory defect (bronchospasm) and diffusion impairment (parenchymal change) should be thought of as consecutive processes in one sense, and yet as distinct and individual changes in another. Certain patients are encountered in whom the diffusing capacity is grossly impaired and ventilatory defect is very slight. We have studied three such patients, who correspond to the patient W. B. S. described by Shepard, Cohn, Cohen, Armstrong, Carroll, Donoso, and Riley (1955). It must be remembered that in such cases the bronchial obstruction and ventilatory defect may follow the changes in the lung parenchyma rather than precede them.

The suggestive finding that the onset of evident right ventricular failure is heralded by a falling diffusing capacity is of interest. The reduction in overall gas diffusion in emphysema may be broadly defined as due to loss of effective blood-surface area. Three changes are probably responsible for this loss: (1) actual loss of lung tissue, leading to direct reduction in blood surface; (2) loss of vascular bed in the remaining tissue; and (3) reduction in effective blood-surface area due to inequality of gas distribution. Only the third of these effects seems likely to be potentially reversible, and it is for this reason that the most likely cause of an improvement in overall D_{CO} in these patients, when such a change is found, is relief or partial relief of bronchospasm. It will be realized that patients with advanced emphysema have no reserve of function at all, and the rate of overall gas diffusion is often so impaired as to permit a maximal oxygen transfer of only 300 to 400 ml. of oxygen a minute. It is obvious that in these circumstances any additional load, such as acute respiratory infection or an increase in bronchospasm, is likely to prove rapidly fatal. The sequence of events suggested by Fig. 12 indicates that careful treatment and supervision of anyone in middle age with bronchospasm might well delay, if not prevent, the changes that are commonly called emphysema. Control of treatment with studies of pulmonary function would add greatly to our knowledge of this group of pulmonary disorders.

Summary

1. Fifty-nine patients considered on clinical criteria to be suffering from pulmonary emphysema have been observed, with respiratory function tests and out-patient supervision, over periods up to five years.

2. Thirteen per cent. of this group died with pulmonary heart failure within

two years, and 22 per cent. within four years. Histological evidence of advanced emphysema was found in all of the nine patients on whom post-mortem examinations were made. The overall mortality for this period is more than four times the value predicted from life insurance tables.

3. During the five-year period 221 estimates of vital capacity, functional residual capacity, and mixing efficiency, and 153 measurements of the diffusing capacity (D_{CO}) were made.

4. Although all these tests of function are of value in diagnosis, only the diffusing capacity (D_{CO}), as measured in this investigation, is a sensitive guide to prognosis.

5. There are two distinct processes in emphysema which usually run concurrently, but which may be independent of one another. The first is bronchial obstruction, and this is mainly responsible for the dominant symptom of this disease, which is dyspnoea. The other, which may be responsible for no symptoms until it leads to heart failure, is the reduction of the pulmonary capillary bed. The latter process, which is most closely related to prognosis, can only be satisfactorily assessed by measurement of the pulmonary diffusing capacity.

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